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SCIENTIFIC AND TECHNICAL ASSESSMENT REPORT ON VINYL CHLORIDE AND POLYVINYL CHLORIDE

ENVIRONMENTAL PROTECTION AGENCY

DECEMBER 1975

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Vinyl chloride (VC) is a chemical of widespread industrial and commercial use. Occupational experience and experimental evidence strongly indicate that it is a carcinogen. Additionally, there is experimental evidence that indicates that it may be a teratogen and mutagen. An increased incidence of liver angiosarcoma, excessive liver damage, and acroosteolysis has been reported among VC workers, and the frequency and severity of the liver pathology is related to the length of exposure. The principal route of exposure is thought to be air inhalation. Sources of increased importance for the general population include food and water. Tumors at multiple and diverse sites have been observed in all species of experimental animals tested for carcinogenicity by inhalation and ingestion of VC. An excess incidence of liver angiosarcoma was observed among VC/PVC (polyvinyl chloride) workers and reproduced in experimental animals with very similar pathology. Liver angiosarcoma was observed in two species of experimental animals after inhalation exposures of VC at the lowest doses tested, 50 ppm (128,000 $\mu g/m^3$), and after ingestion at 16 mg/kg. In addition to the health effects of VC, this document also considres the sources, distribution, and control technology. Emissions of VC from VC/PVC plants are estimated to exceed 100 million kilograms annually, about 90 percent of which is from PVC plants. Installation of currently available controls may be adequate to reduce VC emissions from VC/PVC plants in the order of 90 percent.

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PREFACE

Although this report is issued in the Scientific and Technical Assessment Report Series, it differs in several respects from the comprehensive multi-media format that the Series will usually have because it was nearly completed prior to the creation of the STAR series in August 1974.

The document was prepared by a task force convened under the direction of Dr. F. Gordon Hueter, Special Studies Staff, U. S. Environmental Protection Agency (EPA), Environmental Research Center (ERC), Research Triangle Park (RTP), N. C. Assembly, integration, and production of the report were directed by the Special Studies Staff, ERC-RTP.

In a preliminary assessment of the environmental problems associated with vinyl chloride and polyvinyl chloride, an EPA Task Force in August of 1974 under the direction of the Office of Toxic Substances determined that emissions of vinyl chloride monomer were primarily an air pollution problem. Accordingly, the Office of Air and Solid Waste Management was given the responsibility for an in-depth evaluation of the problem. This report was proposed as a part of this evaluation. The objective was to review and evaluate the current knowledge of vinly chloride in the environment as related to possible deleterious effects upon human health and welfare. An extensive literature review of the toxicology of polyvinyl chloride was not attempted since the primary concern of this report is the vinyl chloride monomer. Information from the literature and other sources has been considered generally through June 1, 1975. A more extensive review of sources, emissions, air quality, and control technology will be available in the *Standard Support-Environmental Impact Statement for Vinyl Chloride.*

In this report, concentrations have been expressed in parts per million (ppm) by volume with the metric equivalent in parentheses. The conversion factor at 25°C and 1 atmosphere of pressure is 1 ppm = 2560 $\mu g/m^3$.

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The document was also reviewed at a meeting with representatives of Federal Departments and Agencies held on December 13, 1974. Officials attending the meeting were:

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Dr. Samuel S. Epstein also participated in the review of the document, as a representative of the National Air Quality Criteria Advisory Committee of the Science Advisory Board.

Review copies of this document also have been provided to other governmental agencies and to industrial and public interest groups.

All comments and criticisms have been reviewed and incorporated in the document where deemed appropriate.

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LIST OF ABBREVIATIONS AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
Ag^+	Silver ion
AKT	Alanine-ketoglutarate transaminase
atm	Atmosphere
BSP	Bromsulphalein
°C	Degree Celsius
cal	Calory
$CH_2:CHCl$ or $H_2C{=}CHCl$	Vinyl chloride monomer
CH_3	Methyl
CH_4	Methane
Cl-C	Chlorinated hydrocarbon
$ClCH_2$-CH_2Cl	1,2-dichlorethane
cm	Centimeter
cm^{-1}	An expression of wavelength used in infrared spectroscopy ($\equiv 1/\lambda$)
cm^2	Square centimeter
CNS	Central nervous system
DBE	Dibromoethane
DDT	Dichlorodiphenyltrichlorethane
ECD	Electron capture detector
EDC	Ethylene dichloride
EPA	U.S. Environmental Protection Agency
ERC	Environmental Research Center
°F	Degree Fahrenheit
FID	Flame ionization detector
ft	Foot
ft^3	Cubic foot
g	Gram
gal	Gallon
GC	Gas chromatography
$HC{\equiv}CH$	Acetylene
HCl	Hydrogen chloride
hr	Hour
IARC	International Agency for Research on Cancer
°K	Degree Kelvin
kg	Kilogram
km	Kilometer
lb	Pound
LDH	Lactic acid dehydrogenase
LD_{50}	Dose lethal to 50 percent of the recipients
m	Meter
m^2	Square meter
m^3	Cubic meter
MFOS	Mixed-function oxidase system
mg	Milligram
ml	Milliliter
mm	Millimeter
mo	Month
mph	Mile per hour
N	Newton
NADPH	Nicotinamide-adenine dinucleotide hydrogenase
NAQCAC	National Air Quality Criteria Advisory Committee
ng	Nanogram
NIOSH	National Institute of Occupational Safety and Health
nm	Nanometer
OSHA	Occupational Safety and Health Administration, U.S. Department of Labor
PCB	Polychlorinated biphenyls
ppb	Part per billion
ppm	Part per million
psia	Pound per square inch, absolute
psig	Pound per square inch, gauge
PVC	Polyvinyl chloride
RTP	Research Triangle Park, N.C.
sec	Second
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic-pyruvic transaminase
SMR	Standard mortality ratio
STAR	Scientific and Technical Assessment Report
TCD	Thermal conductivity detector
THF	Tetrahydrofuran
TLV	Threshold Limit Value (for occupational exposures)
TWA	Time-weighted average
VC	Vinyl chloride
wk	Week
yr	Year
μg	Microgram

ABSTRACT

Vinyl chloride is a chemical of widespread industrial and commercial use. Occupational experience and experimental evidence strongly indicate that it is a carcinogen. Additionally, there is experimental evidence that indicates that it may be a teratogen and mutagen. Precise dose-response relations between vinyl chloride and liver angiosarcoma, and other cancers in man, are not available, as they are not for any other chemical carcinogens. An increased incidence of liver angiosarcoma, excessive liver damage, and acroosteolysis has been reported among vinyl chloride workers, and the frequency and severity of the liver pathology is related to the length of exposure. The principal route of exposure for people living near vinyl chloride (VC) and polyvinyl chloride (PVC) plants is thought to be air inhalation. Sources of increased importance for the general population include food and water.

Tumors at multiple and diverse sites have been observed in all species of experimental animals tested for carcinogenicity by inhalation and ingestion of vinyl chloride. Industrial studies suggest an increased risk of human cancer at multiple sites. An excess incidence of liver angiosarcoma, an extremely rare tumor in man, was observed among VC/PVC workers and reproduced in experimental animals with very similar pathology. Liver angiosarcoma was observed in two species of experimental animals after inhalation exposures of VC at the lowest doses tested, 50 ppm (128,000 $\mu g/m^3$), and by ingestion at 16 mg/kg.

In addition to the health effects of VC, this document also considers the sources, distribution, and control technology. Emissions of VC from vinyl chloride and polyvinyl chloride plants are estimated to exceed 100 million kilograms annually, about 90 percent of which is from PVC plants. Installation of currently available controls, most of which are a basic part of the processing system and serve to recover the reactant or product, may be adequate to reduce vinyl chloride emissions from VC/PVC plants in the order of 90 percent.

SCIENTIFIC AND TECHNICAL ASSESSMENT REPORT ON VINYL CHLORIDE AND POLYVINYL CHLORIDE

1. SUMMARY

This report presents a review and evaluation of the available current scientific data relative to the health and welfare implications of environmental pollution resulting from the production and use of vinyl chloride and polyvinyl chloride. The commercial importance of vinyl chloride (VC) lies primarily in the manufacture of polyvinyl chloride (PVC) resins, which are subsequently manufactured into a large number of useful plastic products.

Derived from petrochemical feedstock and chlorine, VC is a synthetic chlorinated olefinic hydrocarbon monomer. It is a gas at ambient temperature and atmospheric pressure, but is normally shipped and stored as a liquid under pressure. It is flammable, explosive, only slightly soluble in water, and about twice as dense as air.

The concentration of VC entrapped in PVC is dependent upon the production process and can range from 0.1 to about 8 thousand parts per million (ppm). VC can be liberated, particularly when heated, during fabrication.

1.1 HEALTH EFFECTS

Occupational exposure studies have strongly implicated vinyl chloride as a human chemical carcinogen which manifests itself in multiple tumor sites. One of these tumors is a rare liver tumor, angiosarcoma. Similar toxicology studies have verified the occurrence of tumors in other body organs such as the brain and lungs. Other manifestations in humans include acroosteolysis, a degenerative disease affecting bones and finger tips, and liver dysfunction. Experimental studies have shown the potential of VC to be a mutagen and teratogen.

Although actual VC exposure levels responsible for these effects in humans are not precisely known, limited measurements around VC/PVC production facilities indicate that contiguous populations are being exposed to levels of vinyl chloride of potential public health concern. The bases for this concern include, but are not limited to, the following: two community cases of liver angiosarcoma, which are of questionable relationship to vinyl chloride; four confirmed cases of liver angiosarcoma in workers exposed to vinyl chloride, either in final product fabricating plants or during VC manufacture, at levels of exposure as low as 1 to 10 ppm (2560 to 25,600 $\mu g/m^3$), which may be within an order of magnitude of levels observed in ambient air; pathologic noncarcinogenic liver damage in workers exposed to VC in fabricating plants or in post-PVC polymerization phases, which is similar to noncarcinogenic damage seen in workers exposed to much higher levels of VC; and liver damage based upon BSP retention studies of workers involved in polymer processing and workers exposed to TWA concentrations of VC of 50 ppm (128,000 $\mu g/m^3$) for 40 hours a week. None of these data alone provide conclusive evidence that such effects will occur in the general population, but when viewed together they provide a reasonable basis for concern.

The latency period following the onset of occupational exposure is estimated to be about 13 to 20 years. In this regard, there are four reported cases worldwide of liver angiosarcoma following exposure of 3 to 6 years duration: two of these cases have been confirmed by pathologists.

Health implications of residual VC in PVC dust particles have been only superficially studied. Much of the dose-response data on exposure effects of vinyl chloride comes from animal studies using exposure levels of 50 ppm (128,000 $\mu g/m^3$) and above.

1.1.1 Sources and Exposure Mechanisms

The principal route of exposure for persons living in the vicinity of VC emission sources is thought to be air inhalation, although exposure can occur from ingestion of food and water, and from skin contact. There is evidence to indicate that vinyl chloride can exist in drinking water, certain foods, beverages, cosmetics, and other consumer products. Incomplete combustion of PVC products in municipal incinerators can result in the emission of VC as entrapped monomer. Use of vinyl chloride as a propellant in aerosol products recently has been discontinued, so that this source of exposure should decline; however, residual VC-containing products may still be available on the market. Other potential sources of indoor exposure, such as migration of monomer from plastic products, have not been studied. Exposure conditions in the vicinity of PVC product fabricating plants are not yet known.

1.1.2 Human Exposure

Our present knowledge of adverse health effects associated with human exposure to vinyl chloride comes primarily from recent occupational observations, complemented by laboratory animal data.

Between 1949 and 1966, an excess incidence of liver damage (nonmalignant) and acroosteolysis was reported among vinyl chloride workers in Europe. Studies in Germany revealed evidence of liver pathology in a high percentage of PVC production workers with a history of employment ranging from 1.5 to 21 years, but exposure levels responsible for this damage are not known. Since early occupational health studies often reported acute toxic effects (dizziness, headaches, nausea, etc.), it can be assumed that peak exposure levels of several thousand parts per million were experienced at times. Air monitoring data in one group of PVC plants during the period 1950-1959 indicate that time-weighted (8-hour) average exposures in these facilities were in the range 120 to 385 ppm (307,200 to 985,600 $\mu g/m^3$). This may not be typical of exposure in all PVC plants. Peak exposures probably exceeded 1000 ppm (2,560,000 $\mu g/m^3$).

Studies in Europe and the United States since 1966 tend to confirm the earlier findings in Europe. These recent studies include observations of liver damage among workers not directly involved in actual production of PVC. The frequency and severity of liver pathology among PVC workers have been related to the length of exposure, that is, liver damage is most common in workers with an exposure history in excess of 10 years.

To date 15 cases of liver angiosarcoma, a rare form of liver cancer that is considered fatal, have been confirmed among workers with a history of exposure to vinyl chloride in the United States, and 12 such cases have been confirmed in European countries and Canada. Additionally, 11 cases have been reported but have not yet been confirmed. Most, but not all, of these reported cases have been among workers involved directly in PVC production. Cases of liver angiosarcoma have been reported in one worker from the United States and three from Europe exposed to VC, but not directly involved in PVC production. Two community cases of liver angiosarcoma have been reported in persons living in the vicinity of industrial VC emission sources.

While the focus of attention has been on liver angiosarcoma, it should again be noted that a number of industrial studies suggest that the risk of developing other cancers, particularly lung and brain cancer, as well as liver dysfunction and other disorders, also has been related to VC exposure.

1.1.3 Laboratory Exposure

Acute animal toxicity to vinyl chloride was first reported in 1938. Toxic manifestations in experimental animals and man included eye irritation, cardiac irregularities, and increased motor activity, leading to tremor and loss of muscular coordination and finally to narcosis. Short-term acute human experiments (intermittent 5-minute exposures separated by 6 hours over a period of 3 days) with concentrations ranging up to 20,000 ppm (51,200 mg/m^3) produced acute toxic effects at levels about 8000 ppm (20,480 mg/m^3).

Chronic toxic effects due to vinyl chloride in experimental animals include cancer, and damage to the liver, spleen, kidney, lungs, brain, and nerve bundles. Some of the pathological lesions observed in these animal experiments were similar to those later observed in humans engaged in the production and handling of vinyl chloride.

Multiple tumors, including angiosarcoma of the liver and hepatocellular carcinomas, have been observed in rats, hamsters, and mice exposed to vinyl chloride. In rats and mice, liver angiosarcoma has been produced by exposures as low as 50 ppm (128,000 $\mu g/m^3$), the lowest level for which studies have been completed.

1.2 ECOLOGICAL EFFECTS

PVC products are not readily biodegradable. In experimental studies on vegetation, symptoms for ethylene and VC exposure between 10 to 100 ppm (25,600 to 256,000 $\mu g/m^3$) were identical. Vegetational damage around VC manufacturing or processing plants has not been documented.

1.3 PRODUCTION AND USE

The principal use of VC is in the production of PVC, and the principal use of PVC is in the production of a wide variety of useful plastic materials such as floor tile, phonograph records, pipes, and electric insulation. VC also has been used as an aerosol propellant, but this practice has been discontinued. VC was first synthesized in 1837, but the production of vinyl chloride in the United States began in the 1930's. The first important use was in the manufacture of synthetic rubber. Production levels increased rapidly after World War II--the beginning of the industrial chemical era that produced over 20,000 new chemical products. Vinyl chloride production in the United States was less than 45 million kilograms in 1943 and increased to 2.4 billion kilograms in 1973. Based on recent projections, the annual growth rate in the polyvinyl chloride industry is expected to be in the order of 6 percent per year up to 1980, and the annual growth rate in the vinyl chloride industry is expected to be about 3 percent.

In the United States, VC is produced at 17 plants and PVC at 40 plants. Approximately 940 workers are engaged in VC production, and approximately 5600 in PVC production.

1.4 EMISSIONS

Only a very limited amount of VC emission data from industrial sources were available when this report was written. VC loss estimates of approximately 4 percent have been reported, based primarily on material balance studies. Losses to the outdoor atmosphere from industrial sources may occur at a large number of points in the manufacturing processes and will vary depending on the manufacturing facility.

Currently, emissions of vinyl chloride from VC and PVC plants are estimated to exceed 100 million kilograms annually. About 90 percent of all vinly chloride atmospheric emissions are believed to emanate from PVC plants. Data are being obtained on emissions of VC from fabrication plants and from fabricated products, but analyses are not completed at this time. Incineration (without scrubbing) of PVC products results in the emission of hydrogen chloride gas, and under poor combustion (less than 500°C), the entrapped monomer.

1.5 EXPOSURE LEVELS

Data on exposure levels of vinyl chloride in ambient air are limited. Atmospheric measurements in the vicinity of VC/PVC production sources indicate that concentrations are well below 1 ppm (2560 $\mu g/m^3$) in over 90 percent of the cases. One peak value (grab sample) of 33 ppm (84,480 $\mu g/m^3$) has been reported at 0.5 kilometer from the center of one plant. Exposure from other sources (water, food, and other products) has not been quantified.

1.6 MEASUREMENT TECHNIQUES

Available atmospheric vinyl chloride data have been obtained using a variety of sampling and analytical techniques with varying degrees of sensitivity and accuracy. Consequently, the data are not directly comparable in all cases. Standard sampling and analytical procedures have not been established and practiced. Continuous monitoring methods suitable for field use are presently limited to infrared spectrometry. The Wilkes Scientific MIRAN Portable Gas Analyszer has been successfully used in the field. It is limited to a lower detectable limit of 1 ppm (2560 $\mu g/m^3$).

1.7 CONTROL TECHNOLOGY

Currently available technology may be adequate to reduce vinyl chloride emissions from VC plants in the order of 90 percent and from PVC plants by greater than 75 percent. Control of emissions from PVC plants is a more difficult problem, which may require complex process changes. Means of controlling emissions from PVC product fabrication processes are being studied by EPA's Office of Air Quality Planning and Standards.

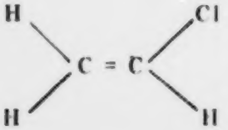
1.8 PHOTOCHEMICAL REACTIONS

Only limited laboratory studies regarding photochemical reactions of vinyl chloride have been made. Vinyl chloride does undergo atmospheric reactions in the presence of nitrogen oxides and solar radiation, although the reaction rate is slower than with other hydrocarbons known to be in the atmosphere. Reaction products of vinyl chloride photooxidation include carbon monoxide, formaldehyde, formic acid, formyl chloride, and hydrogen chloride. The half-life of vinyl chloride in laboratory photochemical chamber experiments has been reported to be 6 hours. The half-life of VC in the ambient atmosphere is not known.

2. CHEMICAL AND PHYSICAL PROPERTIES

2.1 PHYSICAL PROPERTIES

The principal physical characteristics of vinyl chloride are given in Table 2.1.[1] Vinyl chloride (VC) is a chloroolefinic hydrocarbon with a density slightly more than twice that of air, a molecular weight of 62.5, and the structural formula shown below:



Since VC boils at -13.9 °C, it is a gas at normal atmospheric temperature and pressure. It melts at -160°C. Vinyl chloride is highly flammable with a flash point of -78°C (-108°F). The explosive limits are from 4 to 22 percent VC in air by volume. The presence of a chlorine atom in the ethylene molecule changes the dipole moment from 0 to 1.45 Debye units. The corresponding saturated hydrocarbon, chloroethane has a dipole moment of 2.05. Analysis of VC usually reveals trace amounts of organic impurities, such as acetylene, 1,3-butadiene, methyl chloride, vinylidine, and vinyl acetate. Vinyl chloride can be manufactured starting with ethylene or ethyl chloride. The presence of chlorine and a double bond, along with the phenomenon of resonance, cause the reactivity of VC to be less than ethylene and ethyl chloride.

VC is soluble in alcohol, very soluble in ether and carbon tetrachloride, but sparingly soluble in pure water. The quantity of VC that dissolves in water will depend on the partial pressure of the gas above the solution. If the partial pressure of the gas above the water is reduced, VC will escape into the gas phase. Chemical reactions may occur with water impurities, which may tend to inhibit escape of vinyl chloride. Certain salts do have the ability to combine with VC. For example, soluble silver and copper salts increase the solubility of VC in water by forming complexes. In addition to the above salts, VC, like other olefins, will complex with ferrous chloride, platinous chloride, iridium dichloride, mercurous chloride, and a host of other salts. Hence, the residence of VC in water could be affected by the presence of certain salts.

2.2 CHEMICAL PROPERTIES [2-6]

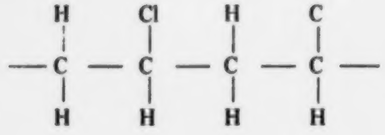
The most important reactions of the olefinic hydrocarbons are related to additions of various compounds to the double bond–for example, hydrogen peroxide, halogens, haloacids, halohydrins, oxides of nitrogen, sulfuric acid, and ozone. Only a few, namely, hydrogen peroxide, oxides of nitrogen, sulfuric acid, and of course ozone, should be of importance in ambient air. The case of formation of free radicals of importance under the conditions of photochemical activity is allylic $> 3° > 2° > 1° > CH_3 >$ vinyl. However, the stability of the free radical is in the reverse order. In some polluted air, particularly in the presence of ozone, reactions would be expected to occur.

In the specific case of VC, the halogen atom attached to the carbon-to-carbon double bond is generally inert. When forced to react, hydrogen chloride is extracted from VC, with the resulting formation of acetylene. Similarly, the hydrogen atoms attached to double bonded carbon atoms are highly stable in substitution reactions. The order of reactivity of the hydrogen atom is allylic $> 3° > 2° > CH_4 >$ vinylic.

Table 2.1. PHYSICAL CHARACTERISTICS OF VINYL CHLORIDE[1]

Formula	$CH_2{:}CHCl$
Molecular weight	62.50
Vapor pressure, 21.1°C	34 psig (2.4 kg/cm² gauge)
Specific volume, 21.1°C	6.2 ft³/lb (387.0 ml/g)
Boiling point, 1 atm	7.0°F (-13.9°C)
Specific gravity, gas 15°C, 1 atm (air = 1)	2.15
Density of liquid, -20°C	0.9834
Critical temperature	317.1°F (158.4°C)
Critical pressure	774.7 psia 52.7 atm or 54.4 kg/cm² absolute
Critical density	0.370 g/ml
Latent heat of vaporization at boiling point	79.84 cal/g
Latent heat of fusion at melting point	18.14 cal/g
Specific heat	
Liquid 20°C	0.38 cal/g
Gas 25°C, 1 atm	0.205 cal/g
Viscosity of liquid, -20°C	0.278 centistoke (0.2734 centipoise)
Flammable limits in air	4.0 to 22.0 percent (by volume)
Autoignition temperature	881.6°F (472°C)
Dielectric constant, 17.2°C	6.26
Surface tension, -20°C	22.27 dynes/cm
Refractive index, $n^{-10}D$	1.4046
Solubility in water, 24°C, 1 atm	0.11 g/100 g water
Conversion factors, 25°C, 1 atm	
1 ppm	2.56 mg/m³
1 mg/liter	391 ppm

The importance of vinyl chloride lies in its ability to polymerize readily in the presence of ultraviolet light or peroxides. The product is polyvinyl chloride (PVC), a highly useful plastic containing the basic structure:



$$\begin{array}{ccccccccc} & H & & Cl & & H & & C & \\ & | & & | & & | & & | & \\ — & C & — & C & — & C & — & C & — \\ & | & & | & & | & & | & \\ & H & & H & & H & & H & \end{array}$$

2.3 REFERENCES FOR SECTION 2

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3. MEASUREMENT TECHNIQUES

3.1 SAMPLING METHODS

3.1.1 Grab Samples

The least expensive approach to monitoring vinyl chloride monomer (VC) concentrations is to collect field samples in a suitable manner and return them to a central laboratory for analysis. Using this approach, samples are collected throughout a suspected problem area with a minimum of power, a minimum of equipment, and with unskilled personnel. Grab samples are collected, as described in the interim procedures,[1] in Tedlar bags or stainless steel canisters. Varying degrees of loss, from 0 to 10 percent per day, have been reported when VC in air was stored in Tedlar bags. Leaky bags may be responsible for losses. Wall losses and permeability of the VC through the walls of the plastic bag do not appear to be a problem with Tedlar bags tested at concentrations of about 10 ppm (25,600 $\mu g/m^3$) or above. VC in pure air appears to be stable. In the presence of nitrogen dioxide, which absorbs solar radiation at about 290 nm, secondary reactions involving ozone (produced by the photolysis of nitrogen dioxide) and VC occur. It may be possible to spike the air sample with a free radical or ozone scavenger to stabilize the VC. Direct photoexcitation of VC is not expected to occur because solar radiation below 290 nm does not reach the lower atmosphere.

Evacuated stainless steel canisters are more rugged, and more easily stored and transported than Tedlar bags. These canisters need only a silicone septum through which a needle can be inserted to evacuate the system to a low pressure. The needle is withdrawn and the septum seals itself, thus maintaining a vacuum until a sample is ready to be taken. At the sampling site, a needle is again inserted, and the air sample is allowed to fill the canister. The needle is withdrawn, and the septum seals itself again. At the laboratory, an aliquot of the sample is removed with a gas-tight syringe and injected directly into a gas chromatograph or other measuring device.

The above procedure yields a short-term concentration. Because the discontinuous nature of the emissions produces pockets of high VC concentrations, this method does not provide an average dosage over a prescribed period. Continuous monitoring is possible with the Wilkes Scientific MIRAN Portable Gas Analyzer, which has a minimum detectable level of 1 ppm (2560 $\mu g/m^3$).

3.1.2 Liquid Scrubbers

Very little information is available concerning the use of liquid scrubbers for the collection of VC. The physical properties of VC are such that it is not easily trapped by a liquid unless some complexation reaction can be produced. Some salts have been reported to complex VC, but they have not been thoroughly investigated for this purpose. For monitoring air pollutants, liquid scrubbers introduce collection, handling, and stability problems that render the technique impractical.

3.1.3 Solid Scrubbers

Solid scrubbers are more easily handled and transported, and have fewer collection problems than liquid scrubbers. Activated charcoal has been useful for the collection of gases and vapors including VC. The capacity of charcoal for VC is limited; hence, problems have resulted from the use of small tubes and large sampling volumes. It is imperative that all newly purchased charcoal be reactivated under nitrogen to maintain its absorption capacity and to remove impurities that may interfere with the analysis. Charcoal was selected as the collection medium in the interim procedure in order to obtain time-weighted averages. Multiple sections were specified to ascertain the quantity of charcoal required under field conditions. It is not yet known how the procedure will respond under field conditions. The quantity of charcoal required to collect VC under the most adverse conditions–such as relative humidity close to 100 percent–needs to be determined.

Other solid scrubbers may be more suitable for VC collection. Hollis and Hayes[2] reported long retention times of low molecular weight hydrocarbons and halogenated hydrocarbons on porous polyaromatic polymer beads. Williams and Umstead[3] determined a number of halogenated hydrocarbons by first concentrating the sample on Porapak Q & S. The materials were thermally desorbed at 100°C for analysis. A microcoulometer with a silver cell was used to determine VC at the 10-part-per-billion (ppb) (25.6-$\mu g/m^3$) level. Lonneman[4] used carbowax under cryogenic conditions to concentrate the sample and analyze concentrations of 100 parts per trillion by gas chromatography. More recently, Bellar[5] successfully concentrated VC from aqueous solution by adsorption on carbonsieve B. Quantitative recoveries were obtained from aqueous solution containing from 5 nanograms (ng) to 5 micrograms (μg) of VC.

All solid scrubbers should be evaluated under simulated field conditions. Commercial permeation devices[6] are available that will generate low levels of VC in air. The resulting mixture is diluted with humid air. In this manner, collection and recovery efficiencies can be more definitively established. The stability of VC on storage in the presence of reactive pollutants in the atmosphere is not known. Some investigators have reported that VC might be polymerizing on these scrubbers. Lajos[7] demonstrated that hydroquinone improved recovery of VC from charcoal without reducing its adsorption capacity.

3.2 SAMPLE PREPARATION

Grab samples present no preparation problems if the amount to be analyzed is greater than 0.02 ppm (51 $\mu g/m^3$), since aliquots are injected directly into a gas chromatograph. If the sample size is sufficient, air samples can be concentrated to detect levels of 0.2 ppb (0.51 $\mu g/m^3$). Brown[1] reports good recoveries from charcoal by extracting with carbon disulfide. This is an excellent solvent for gas chromatography when using the flame ionization detector. This detector gives no response to carbon disulfide under the usual operating conditions, and solvent interfaces are eliminated. Keenan,[8] however, observed that appreciable quantities of VC evaporated into the head space above the liquid when carbon disulfide was used to extract VC. Total recovery of VC in both the liquid and the gas phase was only 80 percent. When Keenan[8] extracted VC with tetrahydrofuran (THF), he obtained a recovery of 88 percent, with less diffusing into the head space than was evident with carbon disulfide.

3.3 ANALYTICAL METHODS

In selecting methods suitable for measuring VC concentrations in ambient air, two factors must be considered. It is desirable that the method employed be capable of measuring in the part-per-million to the part-per-billion range and, because emissions may be discontinuous, it is desirable that the method be capable of responding to high concentration peaks as well as to low, background concentrations.

Designing or describing a measurement technique for a particular purpose requires that three major criteria be satisfied: sensitivity, accuracy, and specificity. In addition, practicality and economics are important considerations in the development of new analytical methods. As a general rule, it is most desirable to measure a pollutant or chemical species directly in the matrix or phase–gas, liquid, or solid–in which the material is generally encountered. This rule precludes any loss or transformation of the material to a nondetectable form.

3.3.1 Spectrophotometry

VC absorbs infrared radiation in the gas phase. The absorption bands at 941 or 917 cm^{-1} have been used to quantify VC. Because interfering substances (Table 3.1) are present in ambient air,[8] the spectrophotometric method is not entirely specific for VC. Multiband measurement and data processing techniques are available

Table 3.1. POSSIBLE INTERFERENCES WITH VINYL CHLORIDE ANALYSIS[8,a]

Compound	Vinyl chloride analytical bands, cm⁻¹ 1626	1020	917	719
Acrylonitrile			W	
Allyl chloride			S	W
Chlorobromomethane				W
Chloroform				W
Ethylene		M	S	
Ethylene dichloride				S
Freon-11			W	
Freon-12	W		S	
Freon-113		S	M	W
Methacrylonitrile	W	W	S	W
Methyl chloroform				S
Methyl chloride		W		M
Methyl methacrylate	W		W	
Perchloroethylene			S	
Styrene			M	
Tetrahydrofuran			M	
Trichloroethylene			M	
Toluene	W		W	S
Vinyl acetate	M	S	W	W
Vinylidine chloride	S			
Vinylidine fluoride	S		S	

[a] W = weak; M = moderate; S = strong.

to correct for these interferences, but additional instrumentation is required. The Fourier transformation system is an excellent example of a refinement in this technique. The cost, however, of this type of system with the refinement would be prohibitive for routine monitoring. Infrared analyzers are not sufficiently sensitive for trace quantities of VC in air since effective optical paths of 20 meters are required to achieve a lower limit of detection of 1 ppm (2560 $\mu g/m^3$). Accuracies of ±10 percent are attainable when the analyzer is properly calibrated with standard gas mixtures. Although the technique is adaptable to continuous monitoring, it is impractical as a multipoint detector of the type generally required to characterize pollutant levels in a problem area. Economics dictate the use of this technique as a research tool or as a laboratory instrument. Air samples, either instantaneous or integrated, can be collected, concentrated if necessary, and returned to a central laboratory for analysis by infrared spectrophotometry.

3.3.2 Gas Chromatography

Gas chromatography (GC) is an analytical technique that separates a complex mixture into its component parts by partitioning the chemical material between a gas and a liquid or solid. The technique is highly popular because of its versatility in solving analytical problems. A wide variety of materials and conditions are available that can be used to achieve separations effectively and inexpensively, even for closely related compounds.[2,9-21]

3.3.2.1 *Column Material*–A list of column materials that have been used to separate vinyl chloride and related compounds is shown in Table 3.2. This by no means is a complete list; there are other systems that can be designed. It is difficult to select the best column material based on the available literature because

Table 3.2 COLUMN MATERIALS AND LIQUID SUBSTRATES SEPARATING VINYL CHLORIDE

Column materials and liquid substrates	References	
Porapak, Q.	Forris	18
Silicone oil DC 550	Levadie	22
Silver nitrate/ethylene glycol	Smith	23
30% silicone oil and polyethylene glycol	Vyakhirev	9
Disodecyl phthalate/carbowax	Hannon	24
Carbowax 4000	Newman	25
25% dibutyl phthalate	Martur	11
5 to 15% silicon rubber SE-30	Hinshaw	12
Silicone grease	Esposito	13
Porapek, -S	Koenig	14
Poly (methyl phenyl siloxane)	Popova	16
Tricresyl phosphate	Vlasov	20
30% dioctyl sebacate	Zalinyan	21
Carbowax 1500 or carbopack A	Brown	1

quantitative data on column efficiencies and height equivalent to a theoretical plate are not generally provided, nor are the objectives of the reported method always similar to the EPA objectives. It is particularly important that VC be separated from hydrocarbons and Freons. Alternatively, more specific detectors must be used in combination with GC.

3.3.2.2 *Detectors*—Detectors that are used in combination with GC columns are also varied. Highly selective and highly sensitive detectors which will detect quantities of material down to 10^{-12} grams (picograms) are available. Completely automated GC instruments are commercially available for environmental monitoring. To measure VC, all that need to be changed on some of these instruments are the column materials and operational parameters. With rare exceptions, measurements are not made continuously, but are made by taking instantaneous samples at short intervals.

The flame ionization detector (FID) is a general purpose detector which responds to most organic compounds, has a wide linear range of several orders of magnitude, and a sensitivity that enables measurement as low as parts per billion. The response to a chemical compound generally varies with the number of carbon atoms. However, certain carbon atoms yield either reduced response or no response when the carbon atom is attached to atoms other than hydrogen, for example, chlorine, oxygen, and sulfur. The FID is insensitive to almost all inorganic gases and compounds. The minimum detectable concentration for VC using a 10-ml sample of gas is 0.01 ppm (25.60 $\mu g/m^3$). When coupled to a GC column to achieve separation, the FID has been the detector of choice because of its sensitivity and minimal cost for the analysis of complex organic mixtures. The GC-FID combination has been used under field conditions, but power requirements and the need for hydrogen gas reduce the practicality of the instrument for routine monitoring.

The thermal conductivity detector (TCD) is mentioned here only for historical purposes. The detector measures changes in the heat capacity of the carrier gas, usually helium or hydrogen, when materials elute from the column. The sensitivity is low when compared with other available detectors. It is not suitable for trace analysis. In addition, the TCD responds to water vapor. This response causes problems in identifying and measuring compounds of interest.

A third group of detectors falls under the general classification of direct current ion chambers. These include argon ionization, helium ionization, micro cross-section detectors, and, most important of all, electron capture detectors. The argon detector consists of two or three parallel electrodes and a radioactive source, usually strontium-90, that excites the argon carrier gas. When chemical compounds elute from the column, they are ionized by the excited argon. Under a voltage gradient of up to 1000 volts per centimeter these ions produce an increase in current flow across the plates or electrodes which is proportional to the concentration of the eluting material The sensitivity is good, but the method is nonspecific and temperamental.

The helium detector is similar in design to the argon detector, except that helium is used as the carrier gas. Voltage gradients as high as 2000 volts per centimeter can be applied across the plates. Tritium is frequently used as the excitation source. This detector is also temperamental, highly sensitive, and nonspecific, but is usually recommended for detecting traces of inorganic gases by gas-solid chromatography.

The electron capture detector (ECD) is similar to the other DC-ion chambers in design. Nitrogen or argon is used as the carrier gas and tritium or nickel-63 is used as the radioactive source. Low voltages (5 to 25 volts) are applied across the plates, usually in a pulsating mode, to eliminate polarization of the electrodes. The detector is specific and highly sensitive to halogenated materials and other materials that absorb electrons. It has a smaller dynamic range and is more temperamental than the FID. The sensitivity of the ECD for VC is poorer than that of the FID because of the presence of a single chlorine atom in the molecule.[10,26] More recent data indicate the sensitivities tabulated in Table 3.3.[26]

The GC-ECD combination has the advantage of requiring only a gas cylinder of nitrogen. Because of its specificity, complete resolution of VC by the GC column is no longer mandatory. Battery operated GC-ECD instruments have been manufactured commercially.

The microcoulometer is a highly sensitive and very accurate detector of chloride ion. The specificity of this detector is increased when used with gas chromatography. Chlorinated hydrocarbons, such as VC, are pyrolyzed as they elute from the column to form gaseous hydrogen chloride which reacts with the solution to precipitate silver chloride and disturbs the electrical balance at the positive, silver electrode. The coulometer regenerates silver ions (Ag^+) until the electrical balance is restored. The detector will respond to any substance which precipitates silver. However, depending on column and pyrolysis conditions, these potential intereferences can be eliminated. With electrochemical efficiency of close to 100 percent, the coulombs generated to restore the balance are proportional to the quantity of chloride ion in accordance with Faraday's law. The detector is highly accurate because the coulomb is a primary standard, and hence, standard reference materials are not absolutely essential. The sensitivity of the detector for VC is of the order of a few nanograms. Electrical power requirements make this system impractical for field use, but it is excellent for laboratory use.

Another electrochemical detector is the conductivity device developed by Coulson for use with gas chromatography.[27,28] The conductivity detector measures either water-soluble ions or gases that produce soluble ions when they react with water. The effluent material is either oxidized or reduced in a small furnace prior to reaching the detector. Depending on the mode of operation, the detector response can be restricted to hydrogen chloride, sulfur dioxide, or sulfur trioxide. High sensitivity is attainable because of the solubility of these gases in water and the high mobility of the hydrogen ion produced. Although sensitivity on the order of a few nanograms is possible, the ultimate sensitivity depends on the geometry or

Table 3.3. SENSITIVITY OF SELECTED DETECTORS USED IN GAS CHROMATOGRAPHY[26]
(grams)

Compound	Thermal conductivity detector	Argon detector	Flame ionization detector	Electron capture detector
Vinyl chloride	2×10^{-6}	1.9×10^{-9}	2.2×10^{-9}	2.3×10^{-9}
Trichloroethylene	2.2×10^{-6}	1.0×10^{-8}	8.5×10^{-9}	2.0×10^{-11}

the cell constant. More recently, a conductivity cell has been designed by Hall[29] which yields higher sensitivities than the Coulson detector. Again, specific detectors reduce the demand on the column to resolve compounds with elution times that are close to those of VC. Power requirements reduce the practicality of this detector under field conditions.

The Beilstein test is a classical flame test for detecting halogens in the presence of copper. This test is the operating principle employed in a flame photometric detector that has been used with a gas chromatograph. The detector uses a photomultiplier tube to measure the characteristic spectrum produced by halogenated substances. The sensitivity of this detector has been enhanced by use of iridium metal.[30] It may be useful without GC as a continuous monitor for gaseous halogenated substances. By using a filter to remove inorganic halogens, this measuring technique would give an index of the total quantity of halogenated materials in a given area. However, to achieve specificity for VC, a GC column would be required. Practicality for field use is equivalent to that of other flame detectors.

Chemiluminescence detectors are used in continuous monitors that measure the quantity and type of light that is produced by reacting certain compounds with ozone–the determination of ozone by reacting with ethylene or the determination of nitric oxide by reacting with ozone. Recently, the monitor has been adapted by EPA scientists to measure VC concentrations. However, a GC column is required to obtain specificity. Current evaluation of the monitor indicates that a sensitivity of a few parts per billion is achievable.

The alkali flame ionization detector and stacked thermionic detectors have also been used as GC detectors to measure halogenated compounds. The mass spectrometer when connected to a GC column is particularly useful in identifying an unknown compound and for unequivocal confirmation of VC. All of these detectors have sensitivities within one or two orders of magnitude of each other. The necessity of one or more gas cylinders and power requirements limit their utility for field use.

3.3.3 Other Analytical Methods

Coulometry has been used to measure olefinic hydrocarbons by reaction with electrogenerated bromine. This technique is not useful for measuring VC in ambient air because of the long reaction time required for the bromination of olefins. In addition, reducing substances such as sulfur dioxide would interfere by consuming bromine. Oxidant would cause a negative interference. Wet chemical methods,[1,31] based on the bromination of VC and then the titration of excess bromine, have also been developed. The sensitivity is only 0.1 mg. Olefins, aromatic compounds that readily add bromine, and reducing agents interfere with this wet chemical method.

Vinyl chloride in air has been analyzed colorimetrically following collection on activated carbon.[28] The VC was extracted and oxidized to formaldehyde, and the formaldehyde determined by reaction with chromotropic acid. Ethylene and methanol interfere with the method. Sensitivity is only a few micrograms.

Polarography[32,33] has been used to measure VC by bromination at the dropping mercury electrode. When this procedure was applied to volatile VC from plastics, it gave a higher value than obtained by the analysis for total chloride. Hence, interfering volatile materials are present. Sensitivity for VC was only 70 micrograms per milliliter.

3.4 AUTOMATED MONITORING

Completely automated monitoring instruments, which are commercially available, can be easily modified to measure vinyl chloride. For example, the carbon monoxide-methane analyzer–which includes a precolumn, a gas chromatographic column, and a flame ionization detector–may be used to quantitate vinyl chloride by simply changing the column packing material and operational parameters. The precolumn removes most of the higher molecular weight hydrocarbons and preserves the integrity of the main column. Using this type of instrument, 5 to 10 samples can be analyzed per hour over a 24-hour period.

Portable gas chromatographs that are less expensive than those described above are commercially available for monitoring VC, but require an attendant. Both the FID and the ECD are available with these instruments and have a reported sensitivity of 0.1 ppm (256 $\mu g/m^3$) VC.

3.5 INTEGRATED SAMPLES USING ADSORBENTS

Integrated values for 8-hour to 24-hour sampling periods can be obtained by using commercially available collection columns. These columns can become a part of a personal monitor, having a self-contained pump worn by a worker, or be part of a permanent installation. During the course of monitoring, a steady stream of sample is drawn through the column containing an adsorbent material, generally activated carbon. The column is capped and returned to a central laboratory for analysis. A flasher technique is used whereby the tube is heated to drive off the collected compounds for gas chromatographic analysis. Another procedure calls for extraction of the vinyl chloride with carbon disulfide. The resulting solution is then analyzed chromatographically using a flame ionization detector. Both methods are sensitive to 1 ppb (2.56 $\mu g/m^3$).[34,35]

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4. ENVIRONMENTAL APPRAISAL

4.1 SOURCES[1,2]

Commercial processors in the United States employ several basic methods in the manufacture of vinyl chloride (VC) monomer and polyvinyl chloride (PVC) polymer resins.

Vinyl chloride monomer production processes employ one of the following:

- The acetylene plus hydrogen chloride reaction.
- The direct chlorination of ethylene and dehydrochlorination.
- The balanced direct and oxychlorination of ethylene and dehydrochlorination.

The two general methods for the production of VC are the acetylene plus hydrogen chloride reaction:

$$\mathrm{HC{\equiv}CH} + \mathrm{HCl} \longrightarrow \mathrm{H_2C{=}CHCl} \qquad (1)$$

and the thermal dehydrochlorination of 1,2-dichloroethane:

$$\mathrm{ClCH_2{-}CH_2Cl} \longrightarrow \mathrm{H_2C{=}CHCl} + \mathrm{HCl} \qquad (2)$$

In the second method, VC plants are integrated with an ethylene dichloride production unit. The overall processes differ primarily in the manner in which the ethylene dichloride is produced.

Nine producers in the United States operate balanced plants in which ethylene is chlorinated by a mixture of hydrogen chloride and air to produce ethylene dichloride. Part of the hydrogen chloride used for this process is in the form of recycled products from the thermal dehydrochlorination of ethylene dichloride. One producer uses the balanced oxychlorination process with the exception that oxygen is used for the oxychlorination reaction sequence.

Three producers use an integrated process in which the ethylene dichloride is produced only by the direct chlorination of ethylene. Hydrogen chloride is recovered from the dehydrochlorination step, but is not recycled into the process.

Polyvinyl chloride is produced at approximately 40 plants in the United States using one of the following processes:

- Suspension polymerization (78 percent of total production).
- Emulsion polymerization (13 percent of total production).
- Bulk polymerization (6 percent of total production).
- Solution (3 percent of total production).

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Gaseous VC is emitted at both VC and PVC resin plants. It is distributed into the atmosphere surrounding the emissions source in patterns that depend on the amount of VC released, the nature of the plant area from which it is released, and the meteorological conditions.

In 1974 approximately 2.6 billion kg of VC and 2.1 billion kg of PVC resin were produced in the United States. VC manufacturers operated at approximately 85 percent of capacity in 1974. Emission data so far supplied to EPA by industry indicate that the total VC escaping to the atmosphere exceeds 100 million kg per year.

Vinyl chloride losses from the average VC plant are estimated to be about 0.45 kg/100 kg of VC produced, and from the average PVC plant approximately 4 kg/100 kg of PVC produced.

Two additional features of the industry are significant in terms of potential VC concentrations in the atmosphere near plants. VC plants are clustered primarily in areas along the Texas and Louisiana Gulf Coast, and some PVC plants are located close to, or even adjacent to, the VC production sites. This "clustering" of plants is greatest in the Pasadena-Deer Park, Texas, region and in the Baton Rouge, Louisiana, area (Figure 4.1).

Vinyl chloride monomer-producing companies are listed in Table 4.1. Included in this table are the companies and their geographical locations, population figures for adjacent communities, and calculated VC emission levels, assuming losses of 4.25 percent. Polyvinyl chloride producers are similarly listed in Table 4.2.

4.2 CONCENTRATIONS IN AMBIENT AIR

Few data are available to characterize the concentration of vinyl chloride in ambient air. In view of the potential danger to human health associated with exposure to vinyl chloride, a preliminary field study was initiated in early 1974 through EPA's Regional Offices to obtain more extensive and reliable data on ambient levels in relation to industrial emission sources. Although air monitoring procedures were established by EPA for this study, the varying degrees of resources and expertise available to the individual Regional Offices produced data that are difficult to compare on a nationwide basis. Based on these limited data, however, ambient concentrations of vinyl chloride exceeded 1 ppm (2560 $\mu g/m^3$) less than 10 percent of the time in residential areas located in the vicinity of plants producing VC or PVC.

Most of the data presented in this section are from instantaneous (grab) samples collected at varying distances from an emission source. As anticipated because of the discontinuous nature of the production processes and resultant emissions, the sampling revealed a wide range of concentrations. The maximum concentration of vinyl chloride observed in ambient air was 33.0 ppm (84,480 $\mu g/m^3$) at a distance of 0.5 km from the center of the plant. In the following discussion, the VC or PVC production plant is identified only by the EPA Regional Office[4] that conducted the sampling.

4.2.1 Region I Plant

Summary data on vinyl chloride concentrations in grab samples taken at varying distances from the center of a production facility in Region I are reported in Table 4.3. Samples taken at sites A through P were collected at 2-hour intervals using Tedlar bags or syringes. The remaining sampling sites are those at which detectable vinyl chloride odors existed; these sites were chosen in an attempt to obtain maximum concentrations. The frequency with which the concentration of vinyl chloride exceeded 1 ppm (2560 $\mu g/m^3$) is shown in the last column. More than 90 percent of the values obtained at this plant were below the minimum detectable concentration (0.06 ppm or 153 $\mu g/m^3$).

The average vinyl chloride concentrations collected at four plant sites in a 24-hour period by charcoal scrubbers are shown in Table 4.4. All data shown in the table were corrected to standard ambient air conditions of 25°C and 1 atmosphere. On May 10, 1974, the average concentration exceeded 1 ppm (2560 $\mu g/m^3$) at site A, which was located 0.3 km from the center of the plant. The site, however, may have been closer to the actual vinyl chloride emission point.

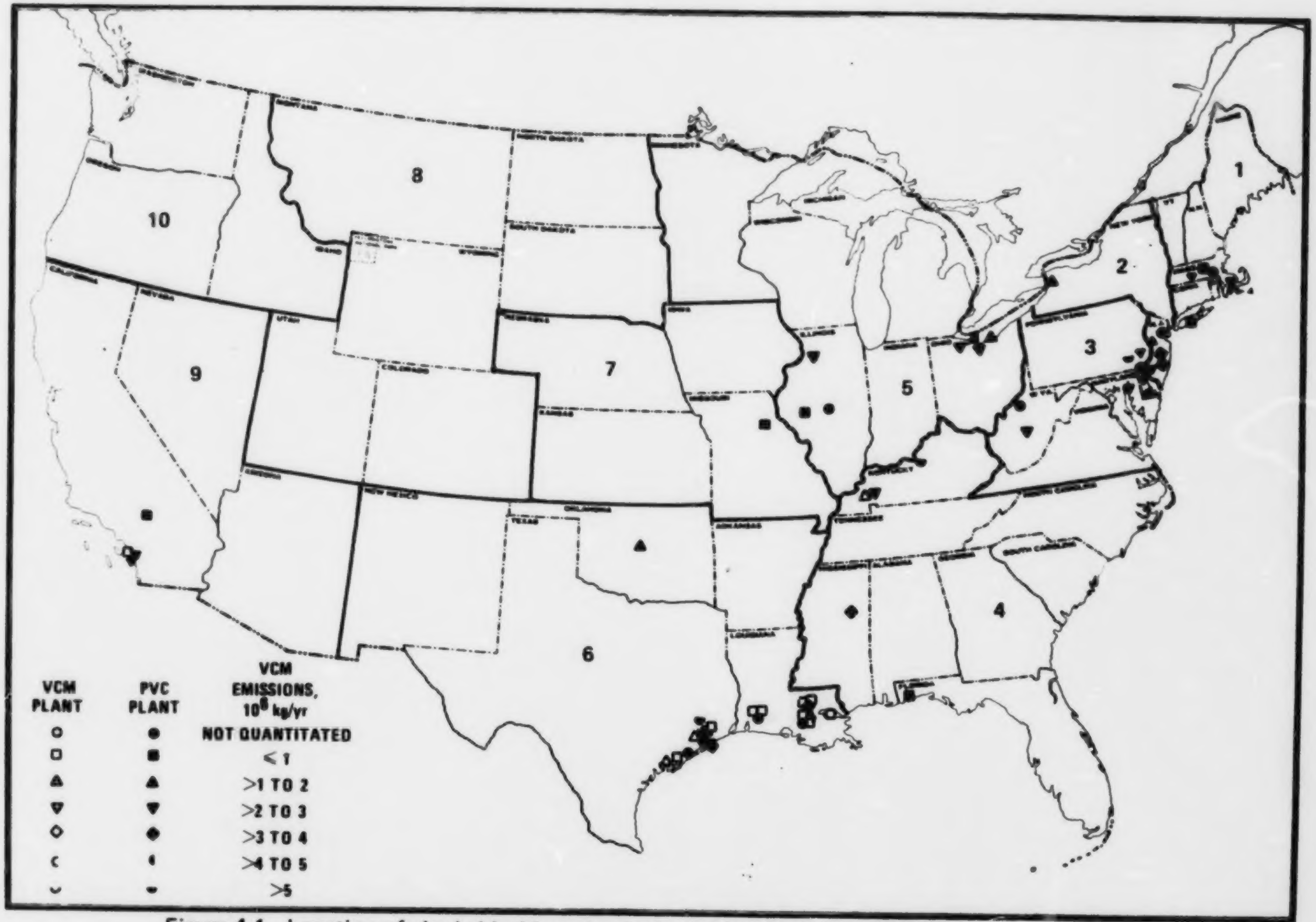
1
2
3
4
5
6
7
8
9
10
VCM PLANT
PVC PLANT
VCM EMISSIONS, 10⁶ kg/yr
○ ● NOT QUANTITATED
□ ■ <1
△ ▲ >1 TO 2
▽ ▼ >2 TO 3
◇ ◆ >3 TO 4
>4 TO 5
>5

Figure 4.1. Location of vinyl chloride and polyvinyl chloride plants. EPA Regions are delineated.

Table 4.1. VINYL CHLORIDE MONOMER PLANT EMISSION DATA

Company and location	City population[a]	Production capacity, June 1974, 10^6 kg/yr	Estimated VC emissions,[b] 10^6 kg/yr	Type of process[c]
Allied Chemical Corp.				
Baton Rouge, La.	165,963[d]	155	0.7	B
American Chemical Corp.				
Long Beach, Calif.	358,633[e]	75	0.4	B
Continental Oil Co.				
Lake Charles, La.	77,998	330	1.5	B
Dow Chemical Corp.				
Freeport, Tex.	11,997[f]	80	0.4	DC
Plaquemine, La.	7,739[g]	155	0.7	DC
Oyster Creek, Tex.	– [f]	320	1.4	B
Ethyl Corporation				
Baton Rouge, La.	165,963[d]	120	0.5	B
Pasadena, Tex.	89,277[h]	70	0.3	DC
B. F. Goodrich Co.				
Calvert City, Ky.	31,627[i]	455	2.0	B
Monochem, Inc.				
Geismar, La.	7,739	135	0.6	B
P.P.G. Industries				
Lake Charles, La.	77,998	135	0.6	B
Guayanilla, P.R.	–	225	1.0	–
Shell Chemical				
Deer Park, Tex.	12,773[h]	410	1.8	B
Norco, La.	–	320	1.4	B
Tenneco Chemical, Inc.				
Pasadena, Tex.	89,277[h]	115	0.5	A
Total		3100	14	

[a] 1970 Census data.[3] The extent of exposure of these populations to VC is not known.

[b] Extrapolated figures based on estimated atmospheric emission loss of 0.45 percent of VC produced in monomer plants and plant operation at full capacity.

[c] Balanced (B)– combination of direct chlorination and oxychlorination process in which the hydrogen chloride produced in cracking is recycled to the oxychlorination process. Direct chlorination (DC). Acetylene (A).

[d] Baton Rouge Parrish (County)–302,031.

[e] Los Angeles County–7,032,075.

[f] Brazoria County–108,312.

[g] Plaquemine Parrish (County)–25,225.

[h] Harris County–1,741,912.

[i] Population given is for Paducah, Ky.

Table 4.2. POLYVINYL CHLORIDE POLYMER PLANT VC EMISSION DATA

Company and location	City population[a]	Type of process[b]	PVC capacity, May 1975, 10^6 kg/yr	VC emissions,[c] 10^6 kg/yr
Air Products and Chemical, Inc.				
Calvert City, Ky.	31,627[d]	Suspension	60	2.2
Pensacola, Fla.	59,507		35	0.9
Stauffer Chemical Co.				
Long Beach, Calif.	358,633[e]	Suspension	20	2.3
Borden, Inc.				
Illiopolis, Ill.	1,122	Suspension and emulsion	65	2.6
Leominster, Mass.	32,939		80	3.2
Continental Oil Co.				
Aberdeen, Miss.	6,157	Suspension and emulsion	120	4.8
Oklahoma City, Okla.	366,481[f]		100	4.0
Diamond Shamrock Corp.				
Delaware City, Del.	2,024	Suspension and emulsion	50	2.0
Deer Park, Tex.	12,773[g]		125	5.0
Ethyl Corp.				
Baton Rouge, La.	165,963[h]	Suspension and emulsion	80	3.2
Firestone Tire and Rubber Co.				
Perryville, Md.	2,091	Suspension, emulsion, and solution (2)	105	4.2
Pottstown, Pa.	25,355		125	5.0
General Tire and Rubber Co.				
Ashtabula, Ohio	24,313	Suspension	55	2.2

Table 4.2. (continued). POLYVINYL CHLORIDE POLYMER PLANT VC EMISSIONS DATA

Company and location	City population[a]	Type of process[b]	PVC capacity, May 1975, 10^6 kg/yr	VC emissions,[c] 10^6 kg/yr
B. F. Goodrich Co.				
Long Beach, Calif.	358,633[e]	Suspension, emulsion, bulk (9)	50	2.0
Henry, Ill.	2,610[i]		100	4.0
Louisville, Ky.	361,472		65	2.6
Avon Lake, Ohio	12,261		120	4.8
Pedricktown, N. J.	–		65	2.6
Georgia Pacific				
Plaquemine, La.	7,739[j]	NA	100	4.0
Goodyear Tire and Rubber Co.				
Plaquemine, La.	7,739[j]	Suspension, emulsion, and bulk	50	2.0
Niagra Falls, N.Y.	85,615		45	1.8
Great American Chemical Corp.				
Fitchburg, Mass.	43,343	Suspension	30	1.2
Keysor-Century Corp.				
Saugus, Calif.	–[e]	Suspension	16	0.6
Monsanto Company (to close in 1975)				
Springfield, Mass.	163,905	Suspension and emulsion	68	2.7
Occidental Petroleum Corp.				
Burlington, N.J.	11,991[k]	Suspension and bulk (32)	75	3.0
Hicksville, N.Y.	48,075		7	0.3
Pantasote Co.				
Passaic, N.J.	55,124	Emulsion	25	1.0
Point Pleasant, W. Va.	6,122		45	1.8
Robintech, Inc.				
Plainsville, Ohio	16,536	Suspension	115	4.6

Shintech, Inc. Freeport, Tex.	–	NA	100	4.0
Stauffer Chemical Co. Delaware City, Dela.	2,024	Suspension	80	3.2
Tenneco Chemicals, Inc.				
Burlington, N.J.	11,991[k]	Suspension and emulsion	75	3.0
Flemington, N.J.	3,917		30	1.2
Pasadena, Texas	89,277[i]		110	4.4
Union Carbide Corp.				
Texas City, Tex.	38,908	Suspension and solution (2)	135	5.4
South Charleston, W.Va.	16,333		75	3.0
Uniroyal, Inc. Painsville, Ohio	16,536	Suspension and emulsion	50	2.0
Certainteed Corp. Lake Charles, La.	77,978	NA	90[l]	4[l]
Total			2752	110.4

[a] 1970 Census data.[3] The extent of exposure of these populations to VC is not known.

[b] The statement on type of process is a preliminary one. Numbers in parentheses indicate estimated production by that process in 10^6 kg/yr. NA = not available.

[c] Extrapolated figures in 10^6 kg/yr based on estimated emission of 4.0 percent VC during polymer production and recovery and full capacity operation. Copolymer production considered the same as homopolymer production.

[d] Population given is for Paducah, Ky.

[e] Los Angeles County–7,032,075.

[f] Oklahoma County–526,805.

[g] Harris County–1,741,912.

[h] Baton Rouge Parrish (County)–302,031.

[i] Henry County–53,217.

[j] Plaquemine Parrish (County)–25,225.

[k] Burlington County–323,132.

[l] Estimated–plant under construction.

Table 4.3. VINYL CHLORIDE CONCENTRATION IN GRAB SAMPLES TAKEN NEAR REGION I PLANT

Site	Distance,[a] km	Number of samples	Maximum concentration, ppm[b]	Mean concentration,[c] ppm	Number >1ppm[d]
A	0.3	17	6.0	0.52	2
B	0.2	16	0.30	0.06	0
C	0.3	9	0.22	0.06	0
D	0.2	9	0.9	0.15	0
E	0.6	11	0.6	0.14	0
F	0.6	9	0.24	0.09	0
G	0.8	8	ND[e]	ND	0
H	0.8	10	ND	ND	0
I	1.1	12	0.40	0.05	0
J	1.6	8	ND	ND	0
K	1.9	7	0.24	0.06	0
L	9.8	8	ND	ND	0
M	1.0	6	ND	ND	0
N	1.0	4	ND	ND	0
O	1.1	5	ND	ND	0
P	0.8	6	0.32	0.11	0
TT	0.2	1	ND	ND	0
UU	0	2	0.24	0.22	0
VV	0	1	ND	ND	0
WW	0.2	3	2.6	1.48	2
XX	0.3	1	0.16	0.17	0
YY	0	1	5.7	6.15	1
ZZ	0.3	1	ND	ND	0

[a] Distance from center of plant to sampling site.
[b] 1 ppm = 2560 μg/m³.
[c] Values corrected to standard temperature of 25°C.
[d] Number of vinyl chloride monomer concentrations above 1 ppm.
[e] Not detectable.

Table 4.4. VINYL CHLORIDE CONCENTRATION IN INTEGRATED 24-hour SAMPLES COLLECTED BY CHARCOAL ABSORBER NEAR REGION I PLANT, 1974

Site	Concentration, ppm[a]		
	May 9	May 10	May 13
A	0.021	1.15	0.165
B	0	0.005	0.020
C	0	0.009	0.029
D	0.141	0.010	0.090

[a] 1 ppm = 2560 μg/m³.

4.2.2 Region IV Plant

At the present time, only the data from the initial study and summary data are available for the plant studied in Region IV. In March 1974, 3 values out of 48 measured exceeded 1 ppm (2560 $\mu g/m^3$) (Table 4.5). The highest concentration was 2.2 ppm (5632 $\mu g/m^3$). The data collected in May 1974 around this plant are summarized in Table 4.6. One instantaneous value of 33 ppm (84,480 $\mu g/m^3$) was observed at a distance of 0.5 km from the plant, and three mean values exceeded 1 ppm (2560 $\mu g/m^3$). The data from the 24-hour integrated samples indicated the highest value to be 0.55 ppm (1408 $\mu g/m^3$) (Table 4.7).

4.2.3 Region VI Plant

Summary data from grab samples taken near an EPA Region VI plant are shown in Table 4.8. The vinyl chloride concentration exceeded 1 ppm (2560 $\mu g/m^3$) in only three of the samples. At the plant property line, the concentration ranged from below the detectable level to 7.8 ppm (19,968 $\mu g/m^3$).

4.2.4 Region IX Plant

Data on vinyl chloride concentrations near a plant in EPA Region IX are presented in Table 4.9. Although more extensive than those for the other Regions, the data provided are not comparable because the samples are 10-minute averages on charcoal instead of instantaneous samples. Under these conditions, concentrations of vinyl chloride as high as 3.4 ppm (8704 $\mu g/m^3$) were found at a distance of 5 km from the plant. Only 12 of the 180 determinations exceeded the 1-ppm (2560-$\mu g/m^3$) level, however. The overall mean value was 0.24 ± 0.44 ppm (614 + 1126 $\mu g/m^3$). Integrated 24-hour values are given in Table 4.10.

Table 4.5. VINYL CHLORIDE CONCENTRATION IN GRAB SAMPLES COLLECTED NEAR REGION IV PLANT, MARCH 1974

Site	Distance,[a] km	Number of samples	Maximum concentration, ppm[b]	Mean concentration, ppm[b]	Number >1 ppm[b]
A	0	6	2.2	0.84	2
B	0.6	3	0.58	0.40	0
C	0.6	4	1.26	0.33	1
D	0.6	6	0.29	0.12	0
E	0.8	3	0.24	0.16	0
F	0.8	15	0.39	<0.17	0
G	0.8	2	–	<0.17	0
H	0.5	1	–	<0.17	0
I	1.3	1	–	<0.17	0
J	1.0	1	–	<0.17	0
K	1.0	2	–	<0.17	0
L	1.3	1	–	<0.17	0
M	4.8	2	–	<0.17	0
N	1.0	1	–	<0.17	0

[a] Distance from center of plant.
[b] 1 ppm = 2560 $\mu g/m^3$.

Table 4.6. VINYL CHLORIDE CONCENTRATION IN GRAB SAMPLES COLLECTED NEAR REGION IV PLANT, MAY 1974

Site	Distance,[a] km	Number of samples	Maximum concentration, ppm[b]	Mean concentration, ppm[b]
A	0.0	6	1.7	0.33
B	0.6	21	5.6	1.6
C	0.6	21	5.8	0.71
D	0.6	19	2.8	0.54
E	0.8	2	0.10	0.07
H	0.5	3	1.2	0.50
I	1.3	2	1.6	1.00
L	1.3	2	ND[c]	ND
N	1.0	1	ND	ND
P	0.6	8	0.08	0.06
Q	0.8	12	1.7	0.34
R	0.5	83	33.0	3.15
S	0.6	1	1.2	1.20
T	1.0	3	0.57	0.21
U	1.0	3	ND	ND
V	0.2	1	ND	ND

[a] Distance from center of plant.
[b] 1 ppm = 2560 $\mu g/m^3$.
[c] ND = not detectable.

Table 4.7. VINYL CHLORIDE CONCENTRATION IN INTEGRATED 24-hour SAMPLES COLLECTED BY CHARCOAL ADSORBER NEAR REGION IV PLANT, 1974

Site	Distance,[a] km	Mean concentration, ppm[b]
MSD	0.6	0.16
NFL	0.6	0.07
SOP	0.3	0.55
DPT	0.2	0.10
CP	1.0	0.01

[a] Distance from center of plant.
[b] 1 ppm = 2560 $\mu g/m^3$.

Table 4.8. VINYL CHLORIDE CONCENTRATION IN GRAB SAMPLES TAKEN NEAR REGION VI PLANT, 1974

Distance,[a] km	Concentration, ppm[b]			
	May 7	May 8	May 9	Maximum
0.0	2.069 0.045 7.814	3.218 0.666 0.003	0.095 0.078	7.8
0.8	0.001 0.002	0.336 ND[c]		0.34
1.2	ND	0.003	ND 0.168 0.001	0.17
1.6	0.002	0.002		0.002
3.2	0.002	0.003	0.023 0.168 0.181	0.18
4.0			ND	ND
4.8	0.002 0.001		ND	0.002

[a] Distance from a chosen center of plant emissions.
[b] 1 ppm = 2560 μg/m^3.
[c] Concentration below detectable level.

Table 4.9. VINYL CHLORIDE CONCENTRATION IN INTEGRATED 10-minute SAMPLES COLLECTED BY CHARCOAL ABSORBER NEAR REGION IX PLANT, 1974[a]

Site	Distance,[b] km	Concentration, ppm[c]														Number >1 ppm
		Run number												Average	Maximum	
		70	71	72	73	74	75	76	77	78	79	80	81			
11	2.4	0.05	0.53	0.08	0.10	0.23	0.05	0.08	0.10	0.04	0.07	0.08	0.08	0.12	0.53	0
12	1.8	0.15	0.06	0.29	0.11	0.15	0.48	0.04	0.19	0.24	0.10	0.11	0.24	0.18	0.48	0
13	2.4	0.24	0.04	0.05	0.03	0.16	0.08	0.02	0.29	0.03	0.85	0.05	0.06	0.16	0.85	0
14	4.5	0.23	0.06	0.04	0.04	0.04	0.05	0.02	0.11	0.32	0.18	0.08	0.25	0.12	0.32	0
15	4.3	0.25	0.31	0.08	0.06	0.12	0.10	0.20	0.55	0.08	0.26	0.07	1.2	0.28	1.2	1
16	5.0	0.25	0.14	0.08	0.13	0.45	0.16	0.05	0.04	1.4	0.17	0.03	0.02	0.25	1.4	1
17	5.0	0.06	<0.05	0.33	0.29	0.21	3.4	0.06	0.53	0.69	0.08	0.02	0.10	0.53	3.4	1
18	1.8	0.05	0.21	0.08	2.7	0.05	0.23	0.03	0.98	0.31	0.12	0.03	0.04	0.41	2.7	1
19	3.1	0.05	0.40	0.10	0.03	0.04	0.16	0.06	0.16	0.33	0.05	0.05	1.7	0.26	1.7	1
20	1.1	0.11	0.02	0.08	0.37	2.1	0.05	0.06	0.36	1.1	0.02	0.02	0.06	0.36	2.1	2
21	1.4	0.11	0.05	0.04	0.26	0.08	0.07	0.22	0.45	0.08	0.24	0.03	0.04	0.14	0.45	0
22	0.8	0.21	0.02	0.02	0.16	0.03	0.03	1.1	0.07	1.0	0.08	0.07	0.84	0.30	1.1	2
23	1.0	0.05	0.05	0.08	0.34	0.11	0.25	0.15	0.04	0.50	0.03	0.05	0.15	0.15	0.50	0
24	1.0	0.11	0.06	1.0	0.08	1.3	0.06	0.07	0.05	0.14	0.02	0.03	1.1	0.33	1.3	3
25	2.1	0.03	0.04	0.10	0.01	0.09	0.09	0.48	0.15	0.03	0.06	0.07	0.33	0.12	0.48	0

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[a] Prepared by EPA's National Field Investigation Center and Region IX Office.

[b] Distance from center of plant.

[c] 1 ppm = 2560 μg/m³.

Table 4.10. VINYL CHLORIDE CONCENTRATION IN INTEGRATED 24-hour SAMPLES COLLECTED BY CHARCOAL ABSORBER NEAR REGION IX PLANT, 1974

Distance,[a] km	Concentration, ppm[b]		
	May 7	May 8	May 9
1.1	0.08[c]	0.07[c]	0.10[c]
1.3	0.08	0.08	0.05
3.1	ND[d]	0.06	0.05
4.3	ND	0.06	0.05
4.5	0.27	0.65	0.27
5.3	0.07	0.04	0.05

[a] Distance from center of plant.
[b] 1 ppm = 2560 $\mu g/m^3$.
[c] 12-hour samples.
[d] Not detectable.

4.2.5 Discussion of Regional Monitoring Data

Since EPA Regional Offices exercised a great deal of latitude in implementing the prescribed procedures, it is difficult to compare data from different plants. All values obtained are expected to be lower than the real value. Grab samples are expected to lose quantities of vinyl chloride monomer because of continuing reaction in the sampling container and leaks. Vinyl chloride monomer losses from these containers are estimated to range from 0 to 10 percent per day. Moreover, losses of VC when using charcoal absorbers are expected to be greater than from the containers. Collection efficiency and recoveries have not been definitively established, but preliminary data indicate recoveries of 71 to 76 percent when extraction by carbon disulfide is used to recover the VC from charcoal. Samples at seven data points were collected in parallel and analyzed by two different laboratories. The resulting values disagreed markedly. The relative standard deviation about the mean ranged from 5 to 140 percent.

4.2.6 Subsequent Vinyl Chloride Monitoring Study

In November 1974, EPA initiated a vinyl chloride monitoring study[5] to obtain measurements of vinyl chloride concentrations and supporting meteorological data at different types of plants emitting vinyl chloride. The primary objective of the study was to obtain information to refine an atmospheric diffusion model for vinyl chloride. To achieve the objective of the study, three types of plants were chosen for monitoring purposes: (1) a PVC plant with the processing equipment enclosed in a building (B.F. Goodrich Chemical Company, Louisville, Kentucky), (2) a PVC plant with processing equipment not enclosed in a building (Continental Oil Company, Aberdeen, Mississippi), and (3) a vinyl chloride plant (Shell Chemical Company, Norco, Louisiana). The distribution of the sampling sites is described in Table 4.11.

The monitoring method consists of a 24-hour sampling procedure which collects vinyl chloride on charcoal absorbers. The vinyl chloride is subsequently extracted with carbon disulfide and resulting solutions are measured chromatographically using a flame ionization detector.

In order to determine bias of the analytical performance, charcoal tubes containing VC which were prepared by the National Bureau of Standards were analyzed with the regular field samples as unknowns. The average bias was -6 percent below standard with a standard deviation of 6 percent. Analysis of field duplicates provided an estimate of uncertainty which includes variables in addition to analytical variability. The average mean difference determined was -1 percent with a standard deviation of 25 percent.

Table 4.11. SITE DISTRIBUTION FOR VINYL CHLORIDE MONITORING STUDY

Location	On or off plant property	Distance from point of reference,[a] meters	Total No. of sites	No. of sites in quadrant			
				0-90°	90-180°	180-270°	270-360°
Louisville, Kentucky	On	< 250	2	1	1		
	On	250 - 400	1			1	
	Off	< 1000	7	6	1		
	Off	> 1000	7	4		1	2
Narco, Louisiana[b]	On	< 250	3 (6)	1 (1)	(1)	1 (2)	1 (1)
	On	250 - 500	7 (4)	3	(4)	4	
	Off	< 1000	3 (5)	1 (5)	1	1	
	Off	> 1000	2	2			
Aberdeen, Mississippi	On	< 250	7	3	1		3
	On	250 - 300	3		1	2	
	Off	< 1000	2				2
	Off	> 1000	3		1	1	1

[a] The stack was chosen as the center of reference for the VC plant at Narco. For the PVC plants at Louisville and Aberdeen, a center of reference was chosen which was estimated to be the approximate center at the emission sources. Since there are multiple point sources in the plant area, a given observation may be located more closely to a point source than the distance indicated from point of reference.

[b] Numbers in parentheses are additional sites operated for approximately 3 weeks.

The study was initiated in November 1974. The monitoring at Aberdeen was discontinued during the last week in March 1975 and the equipment utilized to expand the network in Norco. The additional stations and their distribution are also given in Table 4.11. The study in Norco was discontinued in May 1975 and the stations were moved to Louisville, Kentucky, where monitoring continued until the middle of June. Data from the intensified study in Louisville have not been processed to date and are not included in this report.

During the time of the testing program, the economic recession caused the three plants being monitored (as well as most of the remaining VC and PVC plants) to operate at substantially reduced capacities. This is particularly true of the two PVC plants, which for a large part of the program operated at half capacity; therefore, measurements taken during this time may not reflect the values that might have been obtained under full capacity. Data on operating parameters were collected from the plants and are being compiled.

The results are summarized in Table 4.12. As can be observed, the cumulative frequency distribution is not symmetric and the geometric mean is a closer estimate of the median, or midpoint, of the distribution than the arithmetic mean.

Table 4.12. VINYL CHLORIDE CONCENTRATIONS, CUMULATIVE FREQUENCY DISTRIBUTION

(μg/m³)[a]

Location; on or off plant property	Distance from point of reference,[b] meters	No. obs	Percentile											Arithmetic		Geometric	
			Min	10	20	30	40	50	60	70	80	90	Max	Mean	Std dev	Mean	Std dev
Louisville, Kentucky																	
On	< 250	85	0	0	3	10	18	27	58	84	151	343	708	100.9	156	27.5	6.3
	250 - 400	44	0	3	7	11	18	36	62	91	103	224	814	87.5	143	30.3	5.1
Off	< 1000	288	0	0	3	3	4	7	15	31	56	113	555	43.9	87	10.9	5.3
	> 1000	295	0	0	0	3	3	3	5	7	13	28	220	11.4	22	5.0	3.1
Narco, Louisiana																	
On	< 250	248	0	3	3	5	9	21	49	102	184	47	27,045[c]	262.3	872	27.7	3.3
	250 - 500	227	0	0	0	3	3	3	6	9	23	81	2,875	62.5	288	7.1	4.9
Off	< 1000	152	0	0	3	3	3	3	4	5	9	25	991	21.0	95	5.0	3.3
	> 1000	81	0	0	0	0	3	3	3	3	3	4	53	3.4	5	0.0	1.7
Aberdeen, Mississippi																	
On	< 250	205	0	3	6	23	40	70	134	233	353	1,024	7,560	350.0	822	63.0	8.1
	250 - 300	86	7	43	128	257	302	372	529	667	1,185	1,713	23,430	957.9	1,797	371.7	4.2
Off	< 1000	58	0	0	0	3	4	7	11	20	49	158	1,142	65.5	181	10.7	6.0
	> 1000	134	0	0	0	0	0	0	3	5	9	20	187	11.6	28	3.7	3.4

[a] 1 ppm = 2560 μg/m³.

[b] The stack was chosen as the center of reference for the VC plant at Norco. For the PVC plants at Louisville and Aberdeen, a center of reference was chosen which was estimated to be the approximate center at the emission sources. Since there are multiple point sources in the plant area, a given observation may be located more closely to a point source than the distance indicated from point of reference. These values should not be construed as area averages.

[c] This figure was obtained by a measurement taken between storage spheres in the loading area.

To date, a total of 1903 24-hour VC measurements, not including duplicates, have been obtained. Of these, 21 (1.1 percent) exceeded a VC concentration of 1 ppm (2560 $\mu g/m^3$) and 47 (2.5 percent) exceeded a value of 0.5 ppm (1280 $\mu g/m^3$). The arithmetic average for all values at all sites was less than 0.005 ppm (13 $\mu g/m^3$). This would not necessarily be a representative area value for the plant vicinity, since it does not reflect existing meteorological conditions. The maximum values obtained from the sampling points located outside the plant boundary show that at a distance of less than 1000 m no value exceeded 0.5 ppm (1280 $\mu g/m^3$) and for a distance of greater than 1000 m no value exceeded 0.1 ppm (256 $\mu g/m^3$). However, it cannot be stated unequivocally that these concentrations are not being exceeded at locations not sampled or during other times of the year.

EPA has conducted a monitoring program to determine the vinyl chloride concentrations in the vicinity of PVC fabrication plants. These data currently are being analyzed and a report will be published by the Office of Air Quality Planning and Standards.

4.2.7 Ambient Air Measurements of VC in the Niagra Falls Area

EPA conducted a 6-day survey in the Niagara Falls area to determine the concentration of vinyl chloride in the atmosphere. Samples were collected in residential areas near chemical plants, and in downtown Niagara Falls. The sampling sites are shown in Figure 4.2. Time integrated samples were collected in Tedlar bags and analyzed by gas chromatography with flame ionization detection. The results of the survey are shown in Tables 4.13 through 4.17.

The highest concentration measured was at Site 1–the residence of an individual reported to have liver angiosarcoma, which was, however, later diagnosed as anaplastic carcinoma. Two of the five samples taken in and around the chemical complex contained measureable concentrations of vinyl chloride. Samples taken upwind of the chemical complex, in downtown Niagara Falls, and in Buffalo showed no detectable vinyl chloride.

4.3 DISPERSION MODEL ESTIMATES OF AMBIENT AIR CONCENTRATIONS

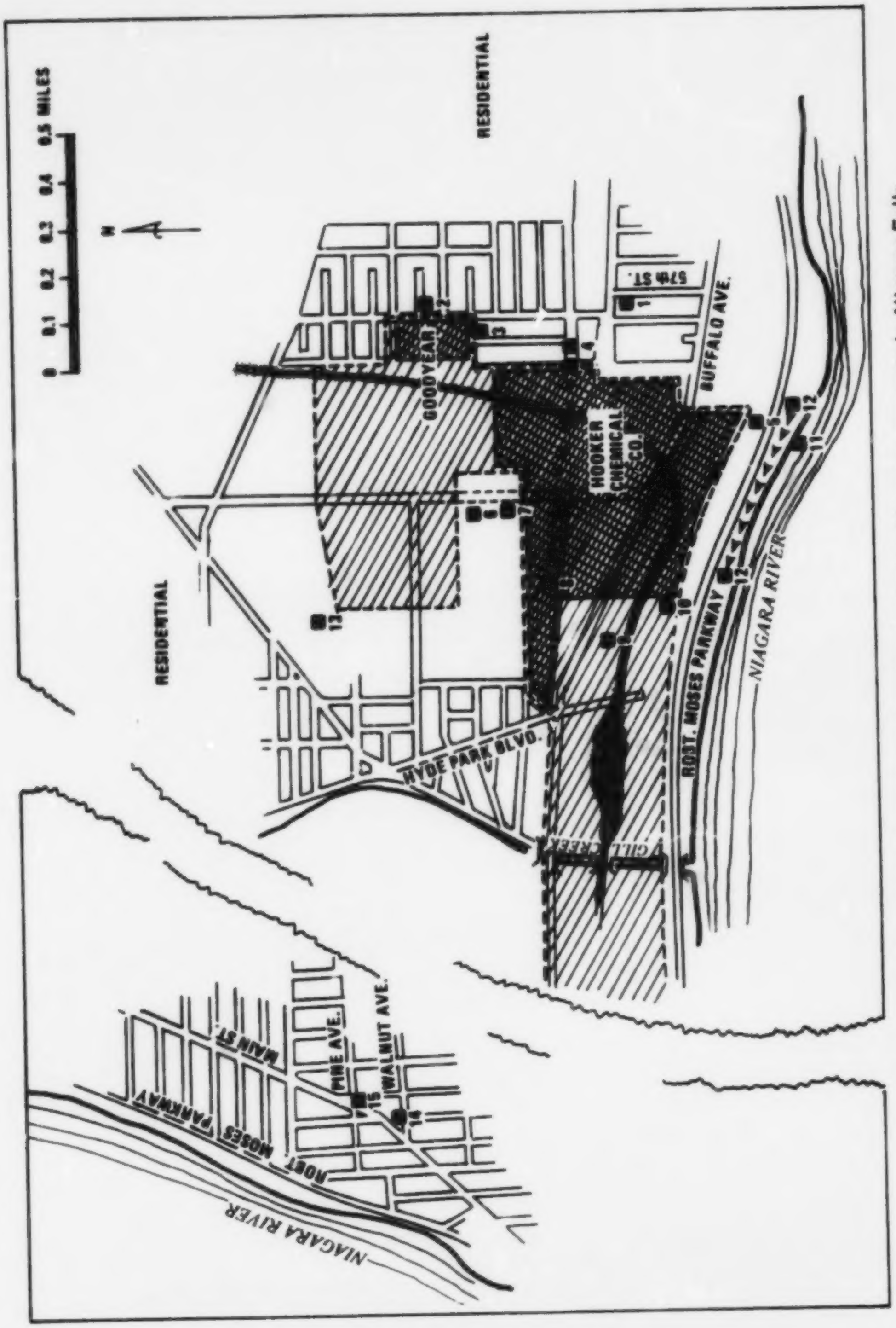
Estimates of vinyl chloride concentrations downwind of two processing plants were made using available emission estimates and representative meteorological conditions. The estimates were made using the Gaussian dispersion model given in EPA's *Workbook of Atmospheric Dispersion Estimates.*[6] Concentration estimates were for 1-hour averaging times. Two hypothetical plants, designated A and B, were considered, with two sets of emission conditions for each plant.

Wind speed was held constant at 2 meters per second for all calculations. Because concentration is inversely proportional to wind speed, a higher wind speed would decrease the estimates; a lower wind speed would increase the estimates. Wind speeds lower than 2 meters per second occur fairly often–on the order of 3 to 15 percent of the time–at most locations.

Three different atmospheric stabilities were considered. Neutral stability occurs when cloudy skies prevail either during the day or at night. Neutral stability also occurs during the transition from unstable daytime conditions to stable nighttime conditions and vice versa. Slightly stable and moderately stable conditions both occur at night with clear skies and light winds. These three meteorological conditions can be expected to occur during quite a number of hours in a given year.

Receptor locations in these model calculations were placed at positions downwind of the approximate center of the sources and off the plant property.

For Plant A, a computation was made considering the emissions from five point sources of varying heights and from one area source. These sources are all located within 200 meters of each other. From Table 4.18, it is seen that the predicted maximum hourly concentrations do not differ greatly for the three stabilities, and are the highest, 4 ppm (10,240 $\mu g/m^3$), for moderately stable conditions. Maximum 24-hour concentrations would be much lower.


0 0.1 0.2 0.3 0.4 0.5 MILES
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HOOKER CHEMICAL CO.
57th ST.
BUFFALO AVE.
ROBT. MOSES PARKWAY
NIAGARA RIVER
HYDE PARK BLVD.
GILL CREEK
MAIN ST.
PINE AVE.
WALNUT AVE.
ROBT. MOSES PARKWAY
NIAGARA RIVER
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Figure 4.2. Locations of sampling sites for vinyl chloride measurements in Niagara Falls.

Table 4.13. AMBIENT AIR SAMPLES FROM 57th STREET, NIAGARA FALLS (Sampling Site No. 1)

Samples from Sampling Site No. 1	Remarks	Vinyl chloride concentration, ppb[a],[b]
1	8:00 p.m. to 8:00 a.m., 6/22, wind north-northwest 10-17 mph.	ND
2	8:00 p.m. to 8:00 a.m., 6/22, wind north-northwest 10-17 mph (sample taken indoors in the upstairs hallway).	ND
3	12:00 midnight to 5:00 a.m., 6/24, wind north-northeast 5-10 mph.	40
4	5:00 a.m. to 10:00 a.m., 6/24, wind north-northeast 7-12 mph.	9
5	12:00 noon to 4:00 p.m., 6/24, wind north-northeast 7-12 mph.	ND
6	4:00 p.m. to 8:00 p.m., 6/24, wind north-northeast 7-12 mph.	9
7	8:00 p.m. to 8:00 a.m., 6/24 - 6/25, wind north 5-10 mph.	6.1
8	9:00 a.m. to 1:00 p.m., 6/25, wind north 5-10 mph.	ND
9	1:00 p.m. to 6:00 p.m., 6/25, wind north-northeast 5-12 mph.	ND
10	7:00 p.m. to 1:00 a.m., 6/25 - 6/26, wind north-northwest 5-10 mph.	6.6
11	1:00 a.m. to 9:00 a.m., 6/26, wind north-northwest 5-10 mph.	27.5
12	10:00 a.m. to 2:00 p.m., 6/26, wind northwest 5-10 mph.	5.5
13	2:00 p.m. to 6:00 p.m., 6/26, wind north-northwest 5-10 mph.	6.6

[a] ND = not detectable.

[b] 1 ppb = 2.560 μg/m^3.

Table 4.14. AMBIENT AIR SAMPLES FROM VICINITY OF GOODYEAR CHEMICAL
(Sampling Sites No. 2 through 7)

Sampling Site No.	Remarks	Vinyl chloride concentration, ppb[a]
2	4:00 p.m. to 4:15 p.m., 6/21, wind north-northwest 5-12 mph.	3
3	11:00 a.m. to 11:10 a.m., 6/24, wind north-northeast 7-12 mph.	0
4	11:15 a.m. to 11:25 a.m., 6/24, wind north-northeast 7-12 mph.	0
5	12:00 noon to 12:30 p.m., 6/24, wind north-northeast 7-12 mph.	0
6	3:05 p.m. to 3:35 p.m., 6/25, wind north-northeast 5-10 mph.	12.7
7	10:00 a.m. to 11:00 a.m., 6/26, wind north 5-10 mph.	0

[a] 1 ppb = 2.560 $\mu g/m^3$.

Table 4.15. AMBIENT AIR SAMPLES FROM VICINITY OF CHEMICAL COMPLEX LOCATED ON BUFFALO ROAD
(Sampling Sites No. 8 through 12)

Sampling Site No.	Remarks	Vinyl chloride concentration, ppb[a]
8	11:25 a.m. to 11:55 a.m., 6/24, wind north-northeast 7-12 mph; sample taken while walking 3/4-mile distance on Buffalo Road.	0
9	11:15 p.m. to 1:30 p.m., 6/25, wind north-northeast 5-10 mph.	0
10	2:15 p.m. to 2:30 p.m., 6/25, wind north-northeast 5-10 mph.	0
11	4:00 p.m. to 4:35 p.m., 6/25, wind north-northeast 5-10 mph.	28.6
12	3:00 p.m. to 4:00 p.m., 6/25, wind northeast 5-10 mph; sample collected over 1.2-mile distance along River Road.	2.5

[a] 1 ppb = 2.560 $\mu g/m^3$.

Table 4.16. AMBIENT AIR SAMPLES OUTSIDE NIAGARA FALLS INDUSTRIAL AREA
(Sampling Sites No. 13 through 15)

Sampling Site No.	Remarks	Vinyl chloride concentration, ppb[a]
13	10:40 a.m. to 11:00 a.m., 6/25, wind north-northeast 5-12 mph.	0
14	11:50 a.m. to 12:10 p.m., 6/25, wind north-northeast 5-12 mph; sample taken over three block area of Main Street downtown Niagara Falls area.	0
15	3:00 p.m. to 3:15 p.m., 6/21, beauty shop, large room, 30 ft by 30 ft, well-ventilated. Sample included a 1-second burst of aerosol hair spray into the room. (Three ppm Freon-12 was observed in sample.)	0

[a] 1 ppb = 2.560 $\mu g/m^3$.

Table 4.17. AMBIENT AIR SAMPLES FROM BUFFALO AREA

Sample No.	Remarks	Vinyl chloride concentration, ppb[a]
1	12:45 p.m. to 1:00 p.m., 6/25, wind north-northeast 7-12 mph, in area of Dearborn Street.	0
2	1:10 p.m. to 1:30 p.m., 6/25, wind north-northeast 7-12 mph, in area of Fargo Street.	0
3	3:30 p.m. to 4:00 p.m., 6/25, wind north-northeast 7-12 mph, in area of Elmer Street.	0

[a] 1 ppb = 2.560 $\mu g/m^3$.

Table 4.18. CALCULATED 1-hour AVERAGE CONCENTRATIONS OF VINYL CHLORIDE MONOMER AT SELECTED DOWNWIND DISTANCES FROM A PLANT WITH MULTIPLE EMISSION SOURCES, PLANT A[a,b]

Distance from plant, km	Concentration, ppm[c]					
	Neutral stability		Slightly stable		Moderately stable	
	No spill	Spill	No spill	Spill	No spill	Spill
0.25	3.5	18.2	3.8	3.8	4.0	4.0
0.4	2.9	29.3	3.4	4.4	3.9	3.9
0.5	2.6	28.2	3.2	6.1	3.7	4.0
0.8	1.7	19.4	2.5	10.9	3.2	7.1
1.0	1.4	14.9	2.1	11.8	3.0	9.5
2.0	0.6	6.0	1.1	8.2	1.9	11.8
3.0	0.4	3.4	0.7	5.4	1.3	9.3
5.0	0.2	1.6	0.3	3.0	0.8	5.9

[a] Emission conditions:

Source type	Emission rate, g/sec	Height of emission, m
Point	18.9	22.9
Point	0.63	15.2
Point	6.3	7.6
Point	8.8	30.5
Point	0.5	38.1
Area[d]	44.1	6
Spill[e]	3783.3	15.2

[b] All calculations assume 2.0 m/sec windspeed.

[c] 1 ppm = 2560 μg/m^3.

[d] Emissions from a 110- by 170-m building through vents and windows about 6 m above the ground.

[e] Spill of 2270 kg of vinyl chloride released in 10 minutes at a height of 15.2 m at 338°K (65°C).

Concentrations resulting from this plant were also estimated for the time at which a reactor is aborted and over 2270 kg of VC is vented to the atmosphere in about 10 minutes. Venting of this type can occur approximately 20 times each year in a PVC plant. Other emissions were assumed to remain the same as in the above calculation. Under these conditions, a maximum hourly concentration of 29 ppm (74,240 μg/m^3) was predicted to occur under neutral stability conditions at 400 meters. Since the other sources contribute less than 3 ppm (7680 μg/m^3) at this point, the vented release contributes about 26 ppm (66,560 μg/m^3). Since the release occurs over only a 10-minute period, a much higher concentration with instantaneous peaks 5 to 10 times this concentration might be expected at 400 meters as the pollutant cloud passes. Concentrations at least five times higher might occur over a 6-to 10-minute averaging time at 400 meters according to these estimates. Beyond 5 km, the impact of a spill would be minimal. For both the spill and nonspill situations, the populations most affected would be those residing within about 2 km of the plant.

For Plant B, one point source and two area sources were considered under two different conditions, average emissions and peak emissions (Table 4.19). Three emission sources are assumed to be located within 300 meters of each other in this calculation. In this case, the maximum concentrations are not increased greatly by an increase of a factor of three in the emissions from the elevated point and by a 2-minute spill from the area source. However, concentrations are nearly doubled at great distances downwind. For Plant B, the maximum concentration, 3.7 ppm (9472 μg/m^3), is almost the same as that from Plant A under normal conditions, 4 ppm (10,240 μg/m^3).

Table 4.19. CALCULATED 1-hour AVERAGE CONCENTRATIONS OF VINYL CHLORIDE MONOMER AT SELECTED DOWNWIND DISTANCES FROM A PLANT WITH MULTIPLE EMISSION SOURCES, PLANT B[a]

Distance from plant, km	Concentration, ppm					
	Neutral stability		Slightly stable		Moderately stable	
	Average[b] emissions	Peak[c] emissions	Average[b] emissions	Peak[c] emissions	Average[b] emissions	Peak[c] emissions
0.2	2.2	2.8	2.8	3.3	3.1	3.6
0.3	1.8	2.4	2.5	3.0	3.1	3.7
0.4	1.6	2.2	2.2	2.7	2.9	3.5
0.5	1.4	2.1	1.9	2.4	2.7	3.2
0.8	1.0	1.7	1.5	2.1	2.2	2.7
1.0	0.8	1.5	1.3	2.0	2.0	2.4
2.0	0.4	0.8	0.7	1.3	1.2	1.9
3.0	0.3	0.5	0.5	0.9	0.9	1.5
4.0	0.2	0.3	0.3	0.7	0.7	1.3
5.0	0.1	0.3	0.3	0.5	0.5	1.0
10.0	<0.1	0.1	0.1	0.2	0.2	0.5
15.0	<0.1	<0.1	<0.1	0.2	0.2	0.3
20.0	<0.1	<0.1	<0.1	<0.1	0.1	0.2

[a] All calculations assume 2.0 m/sec windspeed. 1 ppm = 2560 μg/m^3.

[b] Average emissions:

Point source – 24.0 g/sec at 33.5 m.
Area source 1 – 21.4 g/sec from 150- by 150-m building. Assume emission at 6 m.
Area source 2 – 14.4 g/sec from 180- by 15-m building. Assume emissions at 6 m.

[c] Peak emissions:

Point source – 90.5 g/sec at 33.5 m.
Area source 1 – Same as under average emissions.
Area source 2 – Same as under average emissions *plus* a 2-minute spill of 24,000 g (2000 g/sec).

4.4 REPORTED VC MEASUREMENTS IN WATER AND FOOD

Vinyl chloride has been found in municipal water supplies. EPA, in 1974, initiated an extensive water survey covering 80 public water supplies.[7] These 80 supplies provide a reasonably representative sample of the nation's community drinking water supplies that chlorinate their water and represent a wide variety of raw water sources, treatment techniques, and geographical locations. One major objective of the survey was to characterize, as completely as possible using existing analytical techniques, the organic content of ten finished drinking water supplies which represent five major categories of raw water sources in the United States today.[7] Preliminary data for five of the ten cities are presented in Table 4.20. The remaining analyses should be complete in December 1975. The present data were obtained in most cases from analysis of a single "grab" sample taken from each supply. Sampling conducted at other times of the year might yield different results. The sources of the vinyl chloride found in the Miami and Philadelphia water supplies have not been identified.

EPA is supporting a test program to determine the migration of VC from PVC water pipe. The available results indicate that migration does occur, and that it is a linear function of the residual vinyl chloride level in the pipe itself. Details of this study will be published by the EPA Water Supply Research Laboratory, Cincinnati, Ohio.

Table 4.20. NATIONAL ORGANICS RECONNAISSANCE SURVEY RESULTS FOR SELECTED COMPOUNDS[a]

Compound	Miami, Florida	Seattle, Washington	Ottumwa, Iowa	Philadelphia, Pennsylvania	Cincinnati, Ohio
Organochlorine pesticides[b]	2 ng/1	1 ng/1	2 ng/1	NF	1 ng/1
Organophosphate pesticides	NF	NF	NF	NF	NF
Polychlorinated biphenyls	NF	NF	NF	NF	NF
Herbicides	NF	NF	NF	NF	NF
Haloethers	NF	NF	NF	0.4 μg/1[d]	NF
Vinyl chloride Raw	1.2 μg/1	NF	NF	NF	NF
Finished[c]	5.6 μg/1	NF	NF	0.27 μg/1	NF
Carbon chloroform extract -m	0.9 mg/1	0.1 mg/1	0.7 mg/1	0.4 mg/1	0.7 mg/1

[a] Concentrations: mg/1 = milligram per liter = part per million; μg/1 = microgram per liter = part per billion; ng/1 = nanogram per liter = part per trillion. NF = none found.

[b] Only dieldrin found.

[c] The reason this value is higher than the raw value is unknown at this time.

[d] Represents Bis-2(chloroethyl) ether.

There are limited data on the migration of VC from PVC containers into food, alcoholic and nonalcoholic beverages, and cosmetics. The extent of migration depends upon the residual monomer in the PVC, the length of time of storage, and industrial processes used. Based upon the available migration data, the oral daily human intake of vinyl chloride for Europeans is less than 100 μg.[8] In a study of an analytical method to determine VC concentrations in edible fats, Fuchs et al.[9] found 0.021 mg/kg (21 ppb) in fats which had been stored in containers manufactured from PVC.

Preliminary data have been made available by the Food and Drug Administration (FDA) on vinyl chloride concentrations in some consumer products. The range of concentrations reported is shown in Table 4.21. These data were reported to FDA, but they have not been verified by the agency at this time. The samples were collected prior to January 1, 1975, and therefore may not be representative of products currently available. These data are not adequate to determine a dietary exposure to VC.[10]

4.5 VINYL CHLORIDE EMISSIONS FROM SOLID WASTE INCINERATION

Only limited data are available on vinyl chloride emissions from the incineration of plastics. In a study by the University of Michigan, vinyl chloride was identified as a combustion product from the incineration of plastics.[11] The quantities of combustion products of a representative PVC homopolymer varied as a function of temperature as shown in Table 4.22. The quantity of vinyl chloride also varied with the type of plastics and their polymers.

No data could be found on the concentration of vinyl chloride in the ambient air in the vicinity of municipal incinerators.

Table 4.21. RANGE OF VINYL CHLORIDE CONCENTRATIONS IN SOME CATEGORIES OF CONSUMER PRODUCTS[10]

Product	Range[a]	Sensitivity
Cosmetics[b]	N.D.[c] to 4 ppm	0.1 ppm
Mouthwashes[d]	N.D. to 7 ppm	0.05 ppm
Water pipe (residue)	< 1 to 100 ppm	0.05 ppm
Biologic products	N.D.	0.4 to 0.02 ppm
Vinegar	N.D. to 8.4 ppm	Unknown
Oil	< 10 to 6.5 ppm	Unknown
PVC films	< 1 to < 4 ppm	Unknown
Sheeting	< 1 ppm	Unknown
Meat products	N.D. to 0.4 ppm	Unknown
Cap liners (food and beverage jars)	N.D.	–

[a] Preliminary data—not verified by Food and Drug Administration.
[b] Time in bottle—3 to 48 months.
[c] N.D.—not detectable.
[d] All samples purchased prior to Nov. 1974.

Table 4.22. VARIATION OF COMBUSTION PRODUCTS OF POLYMER A WITH TEMPERATURE[11]

(milligrams per gram of sample)

Compound	25-280°C	280-350°C	350-430°C	430-510°C	510-580°C
Carbon dioxide	–	9.7	181.	244.	237.
Carbon monoxide	–	20.	46.	151.	181.
Methane	–	0.20	1.3	1.8	0.31
Ethylene	0.04	0.33	0.39	–	–
Ethane	–	0.12	0.94	0.41	–
Propylene	0.06	0.11	0.31	–	–
Propane	–	0.08	0.44	0.11	–
Vinyl chloride	0.04	0.25	0.17	0.02	–
1-butene	0.02	0.04	0.08	–	–
Butane	–	0.03	0.20	0.02	–
Isopentane	–	–	0.005	0.001	–
1-pentene	–	0.01	0.03	–	–
Pentane	–	0.01	0.08	0.01	–
Cyclopentene	–	0.02	0.01	–	–
Cyclopentane	–	0.01	0.02	–	–
Hexane	–	0.01	0.05	0.01	–
Methylclopentane	–	–	0.02	–	–
Benzene	24.	6.6	0.35	0.14	–
Toluene	0.12	0.18	0.55	0.03	0.01

4.6 TRANSFORMATION, TRANSPORT, AND REMOVAL

Results on the atmospheric reactions and rates of disappearance of vinyl chloride from the ambient atmosphere are not available. Limited laboratory studies on the stability and persistence of VC in air have, however, been completed. Studies were recently conducted by the EPA Environmental Research Laboratory, Athens, Georgia,[12] to determine the pathways by which vinyl chloride is lost from aquatic systems. Bacterial degradation of VC was found to be negligible, and VC did not affect bacterial growth under test conditions. No sorption to bacteria, algae, or fungi could be detected. Data are not yet available on sorption to inorganic particulate. Equilibrium approximations suggest that under poor transfer conditions sorption to inorganic particulate may be significant.

VC vapor concentrations in containers made of various materials appear to be essentially constant over periods of many days. The peak absorption of VC in the ultraviolet region is far below the solar cutoff (approximately 290 nm) so that VC would not undergo reaction in sunlight in the absence of other reactive chemical species. When irradiated with simulated solar radiation in the presence of nitric oxide and nitrogen dioxide, VC in the part-per-million concentration range reacts to form a variety of products. The reaction products identified include ozone, nitrogen dioxide, carbon monoxide, formaldehyde, formic acid, formyl chloride, and hydrogen chloride.[13]

Although VC should disappear significantly in traveling over longer distances, the conversions anticipated within a few kilometers downwind of emission sources are expected to be small. No mechanism is presently known for removal of vinyl chloride from the air at night. Biological sinks, such as microbiological removal in soil, may be of significance in depletion of vinyl chloride over long time periods; but such sinks would not be expected to be important in terms of urban scale transport of vinyl chloride. Thus, for a first approximation, VC in the immediate vicinity of emission sources can be considered a stable pollutant. The usual meteorological dispersion equations could thus be applied to approximate concentrations in the vicinity of emission sources. Because of strong noctural inversions during the fall and winter, VC buildup from emission sources may be of particular concern during such periods; there are, however, no data on this.

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5. ENVIRONMENTAL EXPOSURE AND RECEPTOR RISK

5.1 EXPOSURE

Human exposure to vinyl chloride may occur from air inhalation, consumption of food, intake of water containing VC, and skin contact. Theoretical considerations suggests that the airborne exposure route represents the greatest source of intake for the population living in the vicinity of emission sources. The higher exposures to VC occur in occupational situations where it is manufactured and where the monomer, a gas at room temperature and atmospheric pressure, is converted to PVC. Workers involved in the polymerization process and in the fabrication of the polymer (PVC) into end products may be exposed not only to vinyl chloride in the gaseous phase, but may also inhale or ingest PVC dust containing temporarily entrapped VC. PVC particles containing vinyl chloride then may be deposited in tissues.[1] There is not adequate information on general or occupational population exposure to PVC particles in the air. Table 5.1 gives the relative importance of various VC sources for the general adult population.

In the past, peak exposures to VC in occupational situations may have exceeded several thousand parts per million at times, for example, during reactor cleaning operations.[2] The highest time-weighted average exposures were probably in the 250- to 500-ppm (640,000- to 1,280,000-μg/m^3) range.[3,4] The threshold limit value (TLV) for vinyl chloride was initially set at 500 ppm (1,280,000 μg/m^3) in 1961 based upon its narcotic properties. After reports of liver damage due to exposures below 500 ppm (1,280,000 μg/m^3) the TLV was reduced to a time-weighted average exposure of 200 ppm (512,000 μg/m^3) for a 40-hour work week, with a 500 ppm (1,280,000 μg/m^3) ceiling for peak exposures.[5,6] When it became evident from animal studies in January 1974 that vinyl chloride produced angiosarcoma of the liver in animals at exposures as low as 250 ppm (640,000 μg/m^3) and when cases of liver angiosarcoma were reported from workers in PVC production plants, an emergency ceiling TLV of 50 ppm (128,000 μg/m^3) was established. Also the U.S. Department of Labor recommended that a permanent standard be set at 1 ppm (2560 μg/m^3).[6] That recommendation has recently been finalized and a permanent standard, which calls for a maximum 8-hour worker exposure of 1 ppm (2560 μg/m^3) of VC, with peak 15-minute exposures not to exceed 5 ppm (12,800 μg/m^3), has been promulgated (May 1974). Since establishment of the 50 ppm (128,000 μg/m^3) emergency standard, additional studies have shown vinyl chloride to be a carcinogen in experimental animals at 50 ppm (128,000 μg/m^3) exposure levels.[6,7]

Table 5.1. RELATIVE IMPORTANCE OF VINYL CHLORIDE SOURCES FOR THE GENERAL ADULT POPULATION (mg VC)

Food[a]	Water[b]	Air[c]	Total
0.002	0.002	0.03	0.034

[a] Assume 2 kg ingested daily containing an average of 0.001 ppm VC by weight, resulting in an intake of 2 μg/day. A World Health Organization report estimates the levels of vinyl chloride in food may be on the order of 1 μg per person per day based upon tentative calculations from a limited range of foods.[10]

[b] Assume 2 liters ingested daily containing 1 ppb of VC. EPA preliminary studies have shown levels of VC in water to range from 0.27 to 5 ppm in two of five cities studied.

[c] Assume inhalation of 20 m^3 per day containing 0.5 ppb vinyl chloride by volume, which is about one half the lowest detectable limit.

The general population in the past may have been exposed to VC through the use of aerosol products (now banned); although the extent of exposure is unknown.[8]

Vinyl chloride concentrations of 2 to 3 ppm (5120 to 7680 $\mu g/m^3$) have been found in manufacturing plant aqueous effluents. Recent studies have shown VC migration from PVC water pipe–the quantity of VC being a linear function of the residual monomer in the PVC pipe.[9] Food, either beverages or solids packaged in PVC containers, may contain vinyl chloride as a result of leaching. The full extent of such a potential exposure is at present unknown. A World Health Organization report tentatively estimates that human intake of vinyl chloride, based upon a limited range of food analyses, is on the order of 1 μg per person per day.[10] It has been estimated that daily oral intake of VC in Europe is less than 100 μg.[11] VC has been shown to be carcinogenic in animals by the oral route.

5.2 RISK TO HUMAN HEALTH

Specification of the possible risk to health among the general population associated with inhalation exposure to vinyl chloride is extremely difficult, in large part due to the lack of information regarding responses to vinyl chloride at ambient dose levels in both animals and man. Further, the data available regarding adverse effects attributable to vinyl chloride in man do not include adequate measures of exposure which may have been responsible for such damage.

In considering the possible risk to human health from vinyl chloride exposure, it is important to keep in mind that with respect to those occupationally exposed, angiosarcoma of the liver, though an invariably fatal disease, is not necessarily the only significant health effect associated with VC exposure. Other cancers may also be involved, and nonmalignant damage to the liver probably affects a far greater proportion of this occupationally exposed population than those who develop angiosarcoma.

To date, angiosarcoma of the liver has been considered an extremely rare disease among the general population. In a survey by the American Cancer Society, only one case of angiosarcoma of the liver was recorded among 78,000 deaths.[12] Shown in Table 5.2 are the results of several studies examining the proportional mortality of liver angiosarcoma among workers exposed to vinyl chloride.[13-16]

Table 5.2. PROPORTIONAL MORTALITY OF LIVER ANGIOSARCOMA AMONG VINYL CHLORIDE WORKERS

Reference	Number of deaths	Number with liver angiosarcoma	Percent with liver angiosarcoma
Monson et al.[13]	161[a]	5	3.1
Nicholson et al.[14]	24[b]	3	12.5
Holder[15]	20[c]	–	–
Wagoner[16]	109[d]	6	5.5
Total	314	14	4.5

[a] Twenty-six deaths occurred among workers at a VCM plant in Calvert City, Ky.; 135 deaths occurred among PVC workers at a polymerization plant in Louisville, Ky.

[b] Deaths occurred among workers at a B.F. Goodrich plant in Louisville, Ky.

[c] Deaths occurred among production employees at one manufacturing location in Michigan who worked for at least 1 year between 1942 and 1960.

[d] Deaths occurred among vinyl chloride polymerization workers at two PVC plants during the calendar period 1950-1973.

It is likely that these reported cases of liver angiosarcoma occurred among workers exposed to levels of vinyl chloride orders of magnitude greater than that which may be found in the ambient air. Compared to the general population (1 case in 78,000), the relative risk of developing liver angiosarcoma among those individuals with previous occupational exposure, by combining all these data, is estimated to be approximately 3000 times greater. Such a relative risk represents a statistically significant difference ($p \ll 0.01$) in the frequency of liver angiosarcoma among those exposed to high levels of vinyl chloride compared to those in the general population.

In attempting to assess trends in incidence of liver angiosarcoma among the population, it is important to recognize that other chemicals besides vinyl chloride may be contributing to such a phenomenon. Included in such a list would be materials with chemical structures similar to vinyl chloride, as well as arsenicals and thorotrast, both of which have already been associated with angiosarcoma of the liver.[17,18]

Other compounds similar in structure to vinyl chloride have been found in high concentrations in households. These compounds, such as trichloroethylene, tetrachloroethylene, trichloroethane, carbon tetrachloride, ethylene chloride, and various Freons, are found in indoor atmospheres in aerosol form. Their sources are cleaning compounds, hair sprays, deodorants, personal hygiene products, inhalants, vaporizers, etc. The toxicity of some of the aerosols are known and the others are suspect. The prolonged exposure to the concentrations measured in homes may have potential carcinogenicity implications.[19]

Vinyl chloride may pose a greater risk to human health than has been measured thus far. The full impact of exposure to vinyl chloride among workers may not be realized for many years, since the greatest number of workers have had onset of exposure only in the last decade and a long latency period is an integral part of angiosarcoma. Certain segments of the population may be at greater risk from exposure than others, such as the very young and aged with little or no activity of the alcohol dehydrogenase enzymes and mixed fluid oxidases which appear to play an important role in accommodating vinyl chloride metabolism. There is also evidence from both animal and epidemiologic studies that the risk of tumor formation can be enhanced by the presence of other chemical agents such as alcohol and certain drugs. It is also possible that other chemicals in the ambient air may enhance the risk of adverse health effects from vinyl chloride.

Thus far angiosarcoma has been used as the major adverse effect for assessing the health risk from vinyl chloride. There is a broader spectrum of dysfunction which has been demonstrated in animal studies and deserves much further study in humans. The mutagenic and teratogenic potential of vinyl chloride in animal studies gives reason to look for comparable effects in humans. The clustering of other types of neoplasms and cancers in the general population living in close proximity to a vinyl chloride production and fabricating plant should also be studied.

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6. UNDESIRABLE EFFECTS

6.1 TOXICOLOGY

6.1.1 Introduction

Although no systematic quantitative assessment of the long-term chronic toxicity of halogenated hydrocarbons has been made, vinyl chloride, trichloroethylene, and vinylidine chloride had been considered among the least toxic of the aliphatic chlorohydrocarbons until recent evidence of carcinogenicity.[1-10] The toxic effects associated with vinyl chloride exposure include narcosis from acute exposure and low grade liver and kidney damage from chronic low exposures. The low exposure effects are similar to those from exposure to other halogenated aliphatic hydrocarbons. In addition, acroosteolysis has been observed among workers exposed to vinyl chloride. This disorder is characterized by degeneration of bones in the fingers and has been associated primarily with direct physical contact with polyvinyl chloride and high levels of vinyl chloride monomer.[1] Acroosteolysis appears to be unique among toxic effects of vinyl chloride when compared to the toxicity of other aliphatic chlorohydrocarbons. The multitumor response and appearance of liver angiosarcoma in experimental animals at lower exposure levels is similar to the cancer response reported in PVC/VC workers.[2-7]

Carcinogenic activity of VC has been confirmed in several species of experimental animals (rodents) and is associated with both subacute and chronic low-level exposure when the experimental period is sufficient in time to permit tumors to appear.[2-7] The appearance of hepatic angiosarcoma in experimental animals, and the discovery of this rare lesion in PVC/VC workers, has served to underscore the predictive value of experimental animal toxicology.[6] Marsteller et al. have recently published a literature review of the toxicology of VC.[11]

6.1.2 Acute Effects

The early experimental toxicology of VC was limited to acute exposures, employed a variety of experimental animals, and was limited to very short exposure periods. The results of these studies have been reviewed by von Oettingen,[12] Mastromatteo et al.,[13] and more recently by Marsteller et al.[11] In general, these investigations, which evaluated exposures that ranged from minutes to hours, suggested that vinyl chloride was of low order acute toxicity, anesthetic in action, and had little capacity to cause injury to the liver or kidneys. These observations led to considering vinyl chloride for use as a general anesthetic.[11] However, the anesthetic effects were often accompanied by cardiac irregularities with some suggestion of cardiac sensitization. Cardiac rhythm irregularities were observed in electrocardiograms of dogs exposed to 100,000 ppm (256,000 mg/m^3) for less than 4 hours. The effective narcotic level in mice exposed to VC for 1 minute ranged from 86,000 to 123,000 ppm (212,480 to 214,880 mg/m^3). Approximately 170,000 ppm (435,200 mg/m^3) was required to induce narcosis in dogs and rabbits over the same exposure period.[12]

Other side-effects indicated that more generalized systemic disturbances are associated with acute exposure. For example, guinea pigs exposed to 5000 ppm (12,800 mg/m^3) of vinyl chloride for a 30- to 60-minute period displayed pulmonary edema and hyperemia of the kidneys and liver.[12] Although all pathological parameters appeared normal in Sherman rats exposed to VC at levels up to 100,000 ppm (256,000 mg/m^3) over a 13-day period, advanced lymphocytic hyperplasia of the spleen was observed.[14] At lower concentrations and extended exposure periods (50,000 ppm or 128,000 mg/m^3; 19 days), the liver size increased in the rats.[14] Pathological examinations revealed congestion at the cellular level in the liver. The morphological alteration observed appears to be consistent with more recent ultrastructure studies.[15] Parasitic cysts were also observed in the liver of these animals, thus confounding conclusions regarding acute effects and systemic damage associated with vinyl chloride.

These results suggest vinyl chloride can induce physiological effects. The morphological alterations observed provided important indications that exposure to vinyl chloride may elicit systemic pathological effects throughout the body. Therefore, effects such as pulmonary edema, tracheal irritation, hyperemia of the liver and kidneys, cardiac arrhythemia, and hyperplastic changes in the spleen and liver may be side effects of acute VC exposure. Furthermore, these effects indicate that functional interaction in various organs and systems of the body may also occur under more chronic low exposure conditions.

More recent acute studies have dealt with modulation of vinyl chloride toxicity by other biologically foreign synthetic chemical compounds (xenobiotics).[15,16] Male Sprague-Dawley rats were pretreated for 7 days by gavage (oral exposure route) with 400 μmoles/kg of body weight of either phenobarbital, a polychlorinated biphenyl (PCB; Acroclor 1254), or hexachlorobenzene and then subjected to 50,000 ppm (138,000 mg/m^3) of vinyl chloride for 6 hours.[15] This single exposure to vinyl chloride produced acute liver damage in the pretreated animals. Animals that were not pretreated and exposed to equivalent levels of vinyl chloride displayed no effects. Animals pretreated with 400 μmoles of 3-methylcholanthrene, spironolactone, or pregnonolone-16-alphacarbonitrile by gavage and exposed to vinyl chloride, 50,000 ppm (138,000 mg/m^3), were also without noticeable liver damage.[15]

The liver injury observed in pretreated animals subsequently exposed to vinyl chloride appears to be specifically associated with structural changes in a basic architectural component of the cell, i.e., endoplasmic reticulum, the subcellular site of enzymes involved in detoxification. Serum transaminase enzymes, used clinically to assess liver damage, increased following vinyl chloride exposure in pretreated animals and were well correlated with induction of specific mixed function oxidase enzymes.[15] This provides indirect evidence that the mixed function oxidase system may be involved in transforming vinyl chloride into a toxic metabolic analog. Ethanol specifically and significantly enhanced the fetal toxicity of vinyl chloride at 500 ppm (1280 mg/m^3) administered to pregnant mice.[16]

These studies lend support to hypotheses that address synergistic interactions and indicate that vinyl chloride liver toxicity is enhanced by some drugs (phenobarbital), alcohol (ethanol), pollutants (PCBs), and pesticidal agents (hexachlorobenzene). While these are for the majority acute studies, they provide important evidence of the nature of pathology that may occur under more chronic low level exposure conditions. A summary of acute effects of vinyl chloride exposure in experimental animals is presented in Table 6.1.

Table 6.1. SUMMARY OF ACUTE EFFECTS OF VINYL CHLORIDE EXPOSURE IN EXPERIMENTAL ANIMALS

1. Vinyl chloride is of low order acute toxicity and anesthetic in action.
2. Anesthetic effects of vinyl chloride are often accompanied by cardiac irregularities, pulmonary edema, trachial irritations, and hyperemia of liver and kidneys. These effects, noted in various species of experimental animals exposed to high levels of vinyl chloride, may be a function of exposure duration.
3. Advanced lymphocytic hyperplasia of the spleen was observed in Sherman rats exposed to 100,000 ppm (256,000 mg/m^3, for 13 days. All other pathological parameters were normal.
4. Pretreatment of experimental animals with drugs (phenobarbitol), alcohol (ethanol), pollutants (PCBs), Acroclor 1254, and pesticide compounds (hexachlorobenzene) potentiates the hepatotoxic effects of VC. VC fetotoxicity is potentiated by alcohol.
5. The mixed-function oxidase system appears to be involved in vinyl chloride metabolism and responsible for its conversion into more toxic metabolites.

6.1.3 Chronic Effects

While investigations of short duration with high exposures are useful in determining lethality and gross toxicity, chronic effects associated with more continuous or repetitive exposures to lower levels of VC are more important in evaluating possible public health hazards. Several investigations designed to assess chronic effects associated with repetitive exposures to lower concentrations of VC began in the early 1960's.

Torkelson et al.[17] reported results of studies using several species of animals (dogs, guinea pigs, rats, and rabbits) exposed to VC levels ranging from 50 to 500 ppm (128 to 1280 mg/m^3). All species exposed to 500 ppm (1280 mg/m^3) of VC for 7 hours/day over a 4.5-month period were normal with respect to outward appearance, growth, and mortality. While several hepatotoxic blood parameters (serum enzymes) were found to be within normal limits at all levels tested, liver size increased in male rats but not in females exposed to levels below 100 ppm (256 mg/m^3). At 100 and 200 ppm (256 and 512 mg/m^3), enlarged liver sizes were observed in both male and female rats. Central lobular degeneration of the liver and renal tubular damage in the kidneys was apparent upon microscopic examination with a dose level to 500 ppm (1280 mg/m^3). Since considerable liver damage is required to alter serum enzyme levels,[18-20] histopathologic changes such as those observed in these studies may have signalled an important parameter in evaluating beginning liver damage not detectable by altered serum enzyme levels. Similar histopathologic effects were observed in the liver of male rabbits exposed to 200 ppm (512 mg/m^3) of VC administered for 7 hours daily over a 6-month period.[17] These effects were not observed in the females.[17] These observations suggest a difference in the response of male and female rabbits to VC, possibly from hormonal differences. While the liver of male and female rats remained increased in size at exposures of 200 ppm (512 mg/m^3) no microscopic pathology was apparent. There were no apparent kidney disturbances noted among the various animals exposed to 200 ppm (512 mg/m^3) of vinyl chloride. Increased liver size was sustained even when exposure concentration and duration were reduced to 100 ppm (265 mg/m^3) for 2 hours daily over the 6-month experimental period. However, while liver-to-body weight ratios at lower dose levels were not statistically different from the ratios in the control group, a trend was suggested. A further reduction in exposure to 50 ppm (128 mg/m^3) for 7 hours a day, 5 days per week over a 6-month period produced no evidence of liver abnormalities either in size or microscopic appearance.[17] Despite the lack of statistical significance, the investigators conducting these studies placed sufficient weight on their observations of subtle liver damage in the several animal species studied to recommend adjustments in the established standards for industrial exposure to vinyl chloride in 1961.[17]

Attempts by Viola et al.[2,21,22] to develop an animal model for investigating the pathogenesis of acroosteolysis revealed convincing evidence of generalized systemic toxic effects in a wide variety of organ systems. These subacute studies provide a more complete description of systemic pathological effects associated with exposure to high concentrations of VC extended over a 12-month period. While attention focused upon the liver of these experimental animals (Wistar rats), pathology was noted in the kidneys, arteries, skin, bones, brain, and nerves. A fibrosclerotic reaction appeared to be a common denominator in the biologically diverse tissues of the various organs examined. A fibrotic lesion in the liver appears to be important in evaluating the precancerous state of liver angiosarcoma and portal cirrhosis associated with vinyl chloride toxicity.[23]

These observations provide evidence that vinyl chloride permeates the body, interferes with membrane structure, and elicits a compensatory repair response marked by endothelial proliferation. This is consistent with morphological observations of vinyl chloride-induced liver damage in animals which were pretreated with various xenobiotics that induce detoxification enzymes present in such cellular membranes.[15] The cellular ultrastructural alterations observed in the liver of animals exposed to vinyl chloride and predisposed animals were similar to that associated with carbon tetrachloride. Carbon tetrachloride produces a peroxidative degradation of structural lipids of membranes and the capacity of this chlorinated compound to produce cellular injury is linked to its reactivity in free-radical reactions.[15] Other reports published in the Russian and European literature provide evidence of alterations in cardiac function, hypertension, and increased adrenalin and neural activity in the brain of several animal species subjected to low, chronic exposure levels of vinyl chloride.[11] These results suggest the possibility of cardiac disturbances and behavioral changes in humans exposed to vinyl chloride under occupational circumstances.[24] Furthermore, workers or other individuals appear to be at a greater risk of liver damage due to exposure to other chemical agents that tend to enhance the hepatotoxic activity of vinyl chloride.

A summary of chronic systemic effects of vinyl chloride observed in experimental animals is presented in Table 6.2.

Although attempts were made to establish a dose-response relationship, few data are available to permit quantitative analysis of the systemic response to VC exposure. Qualitatively, it is important to recognize the significance of repetitive exposures and exposure durations that permit observations of time-dependent response phenomena.[2-9, 14-17]

Table 6.2. SUMMARY OF CHRONIC EFFECTS OF VINYL CHLORIDE EXPOSURE TO EXPERIMENTAL ANIMALS

1. Vinyl chloride is a hepatotoxin. The liver appears to be the most sensitive critical organ. Response includes increased size and weight that may be sex-specific (being noticed more in male than female animals).
2. Central lobular degeneration was observed in the liver of male animals on microscopic exam and was not present in females. Serum enzyme levels used clinically to assess liver damage were normal and not a good parameter to determine early liver damage. Structural damage precedes serum enzyme changes.
3. The circulatory system is disturbed; irregularities in cardiac function; endothelial fibrosis in arteries, and alteration of circulating white blood cell levels and platelets have been observed.
4. Hypertension, increased adrenalin activity, and increased neural activity in the brain have also been observed under chronic exposures.
5. A fibrosclerotic reaction appears to be a common denominator observed in a variety of organs when exposure is of sufficient concentration and duration.

6.1.4 Carcinogenicity

The first evidence of carcinogenic effects associated with exposure to vinyl chloride was reported by Viola et al. [2,21,22] These investigations involved 51 (25 controls) Wistar (AR/IRE) albino male rats (150-g body weight) exposed to 30,000 ppm (76,800 mg/m^3) of VC for 4 hours a day, 5 days week, for 12 months. Under these subacute exposure conditions, tumors were observed in skin, lungs, and bones (Table 6.3).

Although Viola's experiments were not specifically designed to investigate carcinogenicity, there was sufficient evidence of a tumorogenic response to warrant further investigation.[2] Particular attention focused upon the following aspects of the tumorogenicity observed: (1) tumor multiplicity, with neoplastic lesions observed in several tissues and (2) the presence of Zymbal gland tumors. These sebaceous glands, located in the ear of rodents, are particularly responsive to other chemical carcinogens; for example, acetyl-aminofluorine, polynuclear aromatic hydrocarbons such as 9,10-dimethyl-1,2-benzanthracene, urethane, 4-amino-stilbenes, and benzidine.[5]

Since the majority of tumors observed were epidermoid carcinomas of the skin, it was concluded that the cutaneous system was the most susceptible to the tumorogenic effects of VC (Table 6.3 and 6.4). It is important to note the absence of liver angiosarcoma in these animals subjected to levels of VC for nearly half of their lifespan. The exposures used in these experiments were similar to those experienced by PVC reactor cleaners and are similar to the levels which were associated with acroosteolysis.

Table 6.3. TYPES OF TUMORS OBSERVED IN MALE WISTAR RATS EXPOSED TO 30,000 ppm (79,500 mg/m^3) OF VINYL CHLORIDE[2,a]

Wistar rats number	Tumors		
	Skin	Lungs	Bones
1	Mucoepidermoid carcinoma	Adenoacanthoma	Osteochondroma
2,3	Epidermoid carcinoma, keratinizing type	No tumor	No tumor
4	Epidermoid carcinoma, keratinizing type	Adenocarcinoma	No tumor
5	Papilloma, keratotic type	No tumor	Osteochondroma
6	Epidermoid carcinoma	No tumor	Osteochondroma
7	Epidermoid carcinoma	No tumor	No tumor
8	Mucoepidermoid carcinoma	No tumor	Osteochondroma
14	Epidermoid carcinoma	No tumor	No tumor
16,17	Epidermoid carcinoma	Adenocarcinoma	No tumor
21	Epidermoid carcinoma	No tumor	No tumor
22	Epidermoid carcinoma	Adenocarcinoma	Osteochondroma
23	Epidermoid carcinoma	No tumor	No tumor
24	Epidermoid carcinoma	Mucus-producing adenocarcinoma (alveolar cell carcinoma?)	No tumor
25	Epidermoid carcinoma	No tumor	No tumor
26	Epidermoid carcinoma	Squamous cell carcinoma	No tumor
Total	17	6	5

[a] Inhalation exposures were conducted 4 hours/day, 5 days/week over a 12-month period. Scoring only on surviving animals.

Table 6.4. TUMOR INCIDENCE IN MALE WISTAR RATS EXPOSED TO VINYL CHLORIDE[a, 2]

VC		Total animals		Tumors		Total
ppm	mg/m^3		Skin	Lung	Bone	
30,000	79,500	26	17	6	5	25
Controls		25	—	—	—	—

[a] Inhalation of 30,000 ppm (79,500 mg/m^3) vinyl chloride for 4 hours/day, 5 days/week, over a 12-month period.

Due to the evidence of carcinogenicity found in the Viola studies and presented in 1970, a more comprehensive and quantitative series of investigations were initiated in Europe and the United States. These studies were designed to confirm the carcinogenicity of vinyl chloride with emphasis placed on development of dose-response relationships in several species of experimental animals.

In Europe, additional investigations were begun in late 1971 by Maltoni and Lefemine.[5] A series of 14 experiments was designed to investigate the relationship of VC carcinogenicity to the route of administration, exposure concentration, exposure length, exposure frequency, species response variation, and sex- and age-dependent effects. The basic study design placed particular emphasis upon controlled exposure conditions and a definition of a tumor incidence profile from observations compiled over the entire lifespan of the experimental animals (Table 6.5).[25] Vinyl chloride used in these experiments was analyzed as 99.9 percent pure but contained some impurities which are listed in Table 6.6.

A multitumor response was observed with tumors appearing in the circulatory system (liver, vascular bed), excretory system (kidneys), central nervous system (brain), and skin of Sprague-Dawley rats exposed to variable concentrations of vinyl chloride daily (4 hours) for 5 days/week over a 1-year period.[6] Zymbal gland tumors were observed 26 weeks prior to the end of the 52-week treatment period (Table 6.7). These sebaceous gland tumors, which were observed in animals exposed to as low as 500 ppm (1325 mg/m^3), migrate to produce tumors at other body sites such as the lungs. Nephroblastomas of the kidneys and liver angiosarcomas are observed down to 50 ppm (133 mg/m^3). The kidney tumors can metastasize to the liver, lung, spleen, and brain, while liver angiosarcoma metastasized to the lung. The neuroblastoma observed in the brain of rats (Wistar) exposed to vinyl chloride is very similar in appearance to the medulloblastomas that occur in humans.[6] Renal nephroblastoma and liver angiosarcoma were observed in animals exposed to 10,000 ppm (26,500 mg/m^3) at 7 weeks and 12 weeks, respectively, following termination of treatment (52 weeks). The average latency period (the time from the beginning of exposure to diagnosis) for these two tumor types increases with decreasing exposure concentration from 59 weeks for nephroblastoma and 64 weeks for liver angiosarcoma at 10,000 ppm (26,500 mg/m^3) to 135 weeks for both types at 50 ppm (133 mg/m^3).

Liver angiosarcoma was observed in Sprague-Dawley rats at all levels of vinyl chloride exposure investigated. The incidence of liver angiosarcoma decreases with decreasing exposure concentrations as the number of animals exposed remains comparatively constant. It is important to note, however, the appearance of angiosarcoma and other tumors at observed sites at all exposure concentrations studied. Intra-abdominal angiosarcoma as well as angiosarcoma of the liver was reported among the animals exposed to 50 ppm (128 mg/m^3). The appearance of hepatomas in animals exposed to vinyl chloride levels down to 500 ppm (1280 mg/m^3) is particularly noteworthy since these tumors arise from the parenchymal cells of the liver. Liver angiosarcoma is associated more with blood vessels and the lining of blood vessels.

With more than a 60 percent reduction in length of exposure, tumor incidence is reduced and the type of tumors observed changes, but a multitumor response is still observed (Table 6.8). The central nervous system (brain neuroblastomas) appears as equally sensitive to inhaled vinyl chloride at exposures to 2500 ppm (6625 mg/m^3) administered over an 11-week period as over a 52-week period. The only tumor observed at 50 ppm (133 mg/m^3) was an angiosarcoma in the periorbital region of the eye. The Zymbal gland tumors and renal nephroblastoma observed are associated more with higher exposure levels than in the 52-week exposure experiment. There were no tumors of the liver observed at any exposure level of vinyl chloride where the length of exposure was considerably reduced.

Vinyl chloride elicits a multitumor response and liver angiosarcoma in other species of rodents; Wistar rats (Table 6.9), Swiss mice (Table 6.10) and Golden hamsters (Table 6.11). Liver angiosarcoma was observed in Wistar rats and Syrian Golden hamsters at 500 ppm (1280 mg/m^3) and in Swiss mice at 50 ppm (128 mg/m^3). Preliminary analysis 9 weeks after exposure to vinyl chloride under conditions identical to those to which Sprague-Dawley rats were subjected suggests Wistar rats and Golden hamsters may be more resistant to vinyl chloride.

There were no tumors observed in the Wistar rats below 250 ppm (662.5 mg/m^3) 9 weeks after a 52-week exposure. Liver angiosarcoma, nephroblastoma, neuroblastoma of the brain, and Zymbal gland tumors were observed in these animals above 250 ppm (640 mg/m^3). Pulmonary tumors, mammary carcinomas, liver angiosarcoma, vascular tumors of the circulatory system, and epithelial tumors were observed in Swiss mice at 50 ppm (128 mg/m^3).

Vinyl chloride is apparently able to traverse the placental barrier and elicit a carcinogenic response in the offspring of pregnant Sprague-Dawley rats exposed to 10,000 ppm (26,500 mg/m^3) and 6000 ppm (15,900 mg/m^3) during their 12th to 18th day of gestation (Table 6.12). Subcutaneous angiosarcoma was observed in a 24-week-old male and a 22-week-old female offspring. No other tumors were observed.

The preliminary results from Maltoni's ingestion experiments (No. BT11) have revealed the carcinogenic activity of vinyl chloride via the gastrointestinal tract.[26] This study involved four groups of eighty 13-week-old Sprague-Dawley rats (40 males, 40 females). Vinyl chloride, dissolved in olive oil at concentrations of 20 percent, 6.6 percent, and 1.32 percent, was administered 5 times per week to the animals by gastric catheter. Equivalent dosages would have been 50.0, 16.6, and 3.3 mg vinyl chloride per kg of body weight, respectively. Control animals received olive oil only. The scheduled treatment duration was 52 weeks. The results obtained at the end of 50 weeks of treatment are presented in Table 6.13. Caution appears warranted in interpreting these results since vinyl chloride, a gas at room temperature and of low solubility, may have escaped from the oil. However, any loss from the indicated administered dose would point to the ability of vinyl chloride to produce tumors at levels considerably below 50 ppm (128 mg/m^3).

Angiosarcoma of the liver was observed in one animal (one of 40 treated males) that had received a total dose of 863 mg administered over a 52-week period (16.6 mg/kg, 200-g 13-week-old males, 5 days/week, 52 weeks). Angiosarcoma of the thymus gland was also observed in one of the female animals that had received a dosage three times as high. Although differences exist in animal weight, circadian rhythm, absorption, organ distribution, excretion, etc., by alternate exposure routes, the dosage delivered into the gastrointestinal tract by gastric catheter approximates the total dosage received by inhalation that induced both liver angiosarcoma and renal nephroblastoma, i.e. 800 mg (50 ppm; moderate respiration rate of 0.100 liter/min; 4 hr/day, 5 days/week, 52 weeks; Expt. BT1).

Although administered dosages are similar, there may be a significant difference in the period for hepatic angiosarcoma by the two exposure routes. The average latency period reported for the appearance of liver angiosarcoma in Sprague-Dawley rats that inhaled 50 ppm (128 mg/m^3) of vinyl chloride appears to be 135 weeks, i.e. 83 weeks following the end of the 52-week treatment period. Liver angiosarcoma that appeared as a consequence of gastrointestinal absorption was noted 2 weeks prior to the end of the 52-week treatment period. Due to the anatomical location, the functional role of the liver in digestion, and the potential for more efficient absorption of the gastrointestinal tract than the efficiency of the lungs, this

Table 6.5. BASIC STUDY DESIGN OF MALTONI AND LEFEMINE[25]

Exp. no.	Treatment		
	Route	Doses of VC^a	Length
BT1	Inhalation	10,000, 6,000, 2,500, 500, 250, 50 ppm Untreated controls Treated controls: VA 2,500 ppm	4 hr daily, 5 days weekly, 52 wk
BT2	Inhalation	200, 150, 100 ppm Untreated controls	4 hr daily, 5 days weekly, 52 wk
BT3	Inhalation	10,000, 6,000, 2,500, 500, 250, 50 ppm Untreated controls	4 hr daily, 5 days weekly, 17 wk
BT4	Inhalation	10,000, 6,000, 2,500, 500, 250, 50 ppm Untreated controls	4 hr daily, 5 days weekly, 30 wk
BT5	Transplacental	10,000, 6,000 ppm	4 hr daily, 7 days (12th to 18th day of pregnancy)
BT6	Inhalation	30,000 ppm	4 hr daily, 5 days weekly, 52 wk
BT7	Inhalation	10,000, 6,000, 2,500, 500, 250, 50 ppm Untreated controls	4 hr daily, 5 days weekly, 52 wk
BT8	Inhalation	10,000, 6,000, 2,500, 500, 250, 50 ppm Untreated controls	4 hr daily, 5 days weekly, 30 wk
BT9	Inhalation	50 ppm Untreated controls	4 hr daily, 5 days weekly, 52 wk
BT10	Inhalation	10,000, 6,000 ppm Untreated controls	4 hr daily, 5 days weekly, 5 wk; 4 hr daily, 1 day weekly, 25 wk; 1 hr daily, 4 days weekly, 25 wk
BT11	Ingestion	16.6, 33.2, 50 mg/kg body weight in olive oil	5 times weekly
BT12	Endoperitoneal	4.25 mg in 1.0 cm^3 olive oil Controls: 1.0 cm^3 olive oil	4,3,2, times by 2 months and once
BT13	Subcutaneous injection	4.25 mg in 1.0 cm^3 olive oil Controls: 1.0 cm^3 olive oil	1 injection
BT14	Inhalation	10,000, 6,000 ppm	4 hr daily, 5 days weekly, 5 wk
BT15	Inhalation	25, 10, 5 ppm Untreated controls	4 hr daily, 5 days weekly, 52 wk

[a] ppm × 2560 = μg/m^3

Animals						
			No.			
Species	Strain	Age, weeks	Female	Male	Total	Per group
Rat	Sprague-Dawley	13	268	309	577	64-96
Rat	Sprague-Dawley	13	280	265	545	120-185
Rat	Sprague-Dawley	21	262	288	550	60-190
Mouse	Swiss	11	250	260	510	60-150
Rat	Sprague-Dawley	19 (breeders) 12 (embryos)	110	36	146	30-54
Rat	Sprague-Dawley	17	30	30	60	60
Rat	Wistar	11	–	220	220	30-40
Hamster	Golden	11	–	268	268	32-70
Rat	Sprague-Dawley	11	200	200	400	100 300
Rat	Sprague-Dawley	11	420	420	840	120
Rat	Sprague-Dawley	13	160	160	320	80
Rat	Sprague-Dawley	13	150	150	300	60
Rat	Sprague-Dawley	21	80	70	150	75
Rat	Sprague-Dawley	1 day	45	44	89	43-46
Rat	Sprague-Dawley	13	240	240	480	120

Table 6.6. CONTAMINANTS FOUND IN THE 99 PERCENT PURE VINYL CHLORIDE USED IN THE MALTONI AND LEFEMINE EXPERIMENTS[25]

Contaminant	Maximal levels, ppm[a]
Water	100
Acetic aldehyde	5
Acetylene	2
Allene	5
Butane	8
1,3-butadiene	10
Chloroprene	10
Diacetylene	4
Vinyl acetylene	10
Propine	3
Methyl chloride	100

[a] ppm X 2560 = $\mu g/m^3$

route may prove to be a more hazardous exposure route in vinyl chloride carcinogenicity. Thus the importance of food and beverage contamination by VC is again emphasized.

The American investigations[7,27] began after the onset of the European studies and were designed to complement the work of Maltoni and Lefemine.[4-6] While the experimental design does differ to some extent from the design of Maltoni and Lefemine, the early results from the American investigations confirm the capacity of VC to induce hepatic angiosarcoma in mice at an exposure level of 50 ppm (128 mg/m^3) (Table 6.14)[27] Angiosarcoma was also identified in the liver of male rats and hamsters exposed to 2500 ppm (6390 mg/m^3) and one female rat exposed to 200 ppm (530 mg/m^3).[7] Tumors were identified in the lungs, mammary glands, and skin of mice, which is consistent with the evidence of multitumor carcinogenicity of VC found by Viola et al.[2,22] and Maltoni and Lefemine.[4-6] Liver angiosarcomas also were found in Golden Syrian hamsters exposed to gaseous VC, a finding that is consistent with the European studies. No such tumors were observed in the control animals. Although the mortality rate has been high among experimental animals in these studies, it is important to note that angiosarcoma of the liver has been observed in mice exposed to 50 ppm (128 mg/m^3) of VC for only 26 weeks. In the experiments reported by Maltoni and Lefemine,[4-6] liver angiosarcoma was observed at 50 ppm (128 mg/m^3) only after 83 weeks following termination of treatment.

The results from the American and European investigations provide convincing evidence that VC is a chemical carcinogen. It has been shown to induce multiple tumors in various organs and systems in three species (Sprague-Dawley rats, Wistar rats, Syrian Golden hamsters, and mice) of experimental animals at exposure concentrations down to 50 ppm (128 mg/m^3). Angiosarcoma of the liver has been observed in rats and mice at 50-ppm (128-mg/m^3) exposure concentrations in two research laboratories. Wistar rats display a multiple carcinogenic response following inhalation of VC, with tumors appearing in several different organs (bone, kidneys, and skin). However, this strain of rats appears to be more resistant in the development of liver angiosarcoma below 500 ppm (1280 mg/m^3).[2,5] This may be due to limitations imposed by differences in the number of animals exposed. Furthermore, the carcinogenic response in the liver of experimental animals is not restricted to angiosarcoma, since hepatomas also have been observed in experimental animals.[6,28] Only the studies of Maltoni et al.[5,26] are sufficiently advanced to provide some information in regard to dose-response relationships of VC. The information available from several studies indicates that VC carcinogenicity is dose-dependent. Total tumor incidence increases with increasing concentrations of VC and also is a function of exposure duration (Tables 6.7 and 6.8). In fact, the results of the Maltoni et al. studies[4,26] suggest that liver angiosarcoma may be more dependent upon duration of exposure than upon the concentration of VC administered since it was not observed under reduced exposure conditions. A comparison of the various tumors observed in experimental animals and in man is presented in Table 6.15. This table fails to note the epidemiological evidence of brain tumors observed among VC/PVC workers.[24]

Conclusions drawn by Maltoni and Lefemine on vinyl chloride carcinogenicity are presented in Table 6.16.

An additional important toxicological consideration of vinyl chloride, its metabolites, and its structural analogs (trichloroethylene; vinylidine chloride) is the evidence of transplacental carcinogenicity. The results of Maltoni and Lefemine demonstrate transplacental carcinogenicity of vinyl chloride (6000 to 10,000 ppm, or 15,400 to 25,600 mg/m^3).[25] This indicates that vinyl chloride or metabolic conversion products traverse the placental barrier. Trichloroethylene, a structural analog and a positive carcinogen in experimental animals, has been shown to traverse the placental barrier in humans.[29] Although the study involved administering trichloroethylene mixed with nitrous oxide as an anesthetic without specifying dosage, levels of trichloroethylene were determined in maternal and fetal blood at the time of delivery. The results clearly demonstrated transplacental transfer of trichloroethylene. The author also noted the effects that may be attributed to the mode of administration. Intermittent exposure leads to the metabolic conversion of trichloroethylene to trichloroacetic acid and trichloroethanol in the mother while unmetabolized trichloroethylene accumulates in fetal circulation. One explanation for this accumulation is that the fetus is very poor in enzymes capable of metabolizing halogenated compounds such as trichloroethylene and vinyl chloride. Since this study preceded the recent evidence of trichloroethylene and vinyl chloride carcinogenicity, no attention has apparently been given to followup studies as to tumors in the mothers or offspring. There is evidence that vinyl chloride is a transplacental carcinogen and can apparently reduce litter size and increase resorptions of fertilized ova in experimental animals.[16] This suggests that such effects may have heritable genetic consequences.

In vitro mutagenic bioassays have shown that vinyl chloride, vinylidine chloride, and presumed metabolites of vinyl chloride–chloroethylene oxide, chloroacetaldehyde, and chloroethanol–are mutagenic.[30-32] Vinyl chloride exposures used in the microbial test systems were 0.2, 2.0, and 20 percent or 2000, 20,000, and 200,000 ppm (512, 53,000, and 530,000 mg/m^3). While these levels are more relevant to past exposures experienced in the workplace and operating rooms, qualitatively, the results suggest potential hazards at lower levels. These data, considered in light of the teratogenic evidence in whole animals at 500 ppm (128 mg/m^3) of vinyl chloride and the enhanced effects observed with ethanol,[16] indicate that these compounds warrant serious concern for health hazards associated with exposure to vinyl chloride (and related compounds), particularly for members of the general population predisposed by pregnancy. Preliminary evidence of such a hazard has been detailed in the work of Infante, who has shown an increased incidence of birth defects (spina bifida, cleft palates, etc.) in a community near a polyvinyl chloride production plant.[33] Caution is warranted in drawing causal conclusions with respect to these birth defects and location of the PVC facility since there are no monitoring data to document exposure to vinyl chloride, but this report demonstrates the need for further investigation.

Table 6.7. CARCINOGENIC EFFECTS OF INHALED VINYL CHLORIDE 83 WEEKS FOLLOWING EXPOSURE (Exp. BT1)[6]

	Animals with tumors							
	Animals (Sprague-Dawley rats)		Zymbal gland carcinomas[c]			Nephroblastomas[e]		
Treatment[a]	Total	Corrected number[b]	No.	%[d]	Average latency time, weeks	No.	%[d]	Average latency time, weeks
10,000 ppm	69	61	16	26	50	5	8	59
6,000 ppm	72	60	7	12	62	4	7	65
2,500 ppm	74	59	2	3	33	6	10	74
500 ppm	67	59	4	7	79	4	7	83
250 ppm	67	59	–	–	–	6	10	80
50 ppm	64	59	–	–	–	1	2	135
No treatment	68	58	–	–	–	–	–	–
Total	577	464	29	–	–	26	–	–

[a] The animals were treated by inhalation for 4 hours daily, 5 days weekly, for 52 weeks. ppm x 2560 = $\mu g/m^3$.

[b] Animals alive after 26 weeks, when the first tumor (a Zymbal gland carcinoma) was observed. The percentages are referred to the corrected number.

[c] Metastases to lung.

[d] Percentage of corrected number.

[e] Metastases to liver, lung, spleen, and brain.

[f] Metastases to lung.

[g] Several cases of breast fibroadenomas and adrenal and pituitary tumors (generally adenomas) have not been considered, since their distribution in the different groups does not vary.

[h] Several animals with two or more tumors.

[i] One angiosarcoma of the lips; one angiosarcoma of the nose; one intra-abdominal angiosarcoma (next to liver).

[j] One angiosarcoma in subcutaneous fibrosing angioma; one ossifying parauricular angiosarcoma; one intra-abdominal angiosarcoma (next to liver).

[k] Two intra-abdominal angiosarcomas (one next to spleen and one next to ovary); one ossifying angiosarcoma of the neck.

Animals with tumors									
Angiosarcomas				Subcutaneous angiomas, no.	Skin carcinomas, no.	Hepatomas, no.	Brain neuroblastomas, no.	Other type and or site,[g] no.	Total,[h] no.
	Liver[f]								
No.	%[d]	Average latency time, weeks	Other sites, no.						
9	15	64	3[i]	4	3	1	7	7[o]	38
13	22	70	3[j]	3	1	1	3	8[p]	31
13	22	78	3[k]	3	1	2	5	4[q]	32
7	12	81	2[l]	1	1	3	–	4[r]	22
4	7	79	2[m]	–	4	–	–	3[s]	16
1	2	135	1[n]	1	1	–	–	9[t]	10
–	–	–	–	–	–	–	–	10[u]	6
47	–	–	14	12	11	7	15	45	155

[l] One pulmonary angiosarcoma; one angiosarcoma of the uterus.

[m] One intra-abdominal angiosarcoma (next to spleen); one intrathoracic ossifying angiosarcoma.

[n] One intra-abdominal diffused angiosarcoma.

[o] Two Zymbal gland adenomas; three mammary carcinomas; one neurilemmoma; one ovarian cystoadenocarcinoma.

[p] Four Zymbal gland adenomas; one salivary gland adenocarcinoma; two hepatic and one peritoneal angiomas.

[q] One Zymbal gland adenoma; one mammary carcinoma; two ependymomas.

[r] One mammary carcinome; two lymphomas; one pulmonary fibrosarcoma.

[s] One Zymbal gland adenoma; one mammary carcinoma; one lymphoma.

[t] Three Zymbal gland adenomas; two mammary carcinomas; one subcutaneous angiopercitoma; three uterine adenocarcinomas (one with sarcomatous component).

[u] One invasive acanthoma of Zymbal gland; one subcutaneous fibrosarcoma; two peritoneal fibroangiomas; two uterine adenocarcinomas (one with sarcomatous component); one uterine leiomyosarcoma; one ovarian fibrosarcoma; one pulmonary rhabdomyosarcoma; one lymphoma.

Table 6.8. CARCINOGENIC ACTIVITY OF INHALED VINYL CHLORIDE 69 weeks FOLLOWING A REDUCED EXPOSURE PERIOD (BT3)[6]

	Number of animals (Sprague-Dawley rats)		Number of animals with tumors[b]						
			Zymbal gland carcinomas	Nephroblastomas	Angiosarcomas		Brain neuroblastomas	Other type and/or site[c]	Total[d]
Treatment[a]	Total	Survivors			Liver	Other sites			
10,000 ppm	60	9	6(16)	–(5)	–(9)	1[e] (3)	6(7)	3[g] (15)	15(40)
6,000 ppm	60	16	4(7)	–(4)	–(11)	–(3)	2(3)	7[h] (9)	10(27)
2,500 ppm	60	33	1(2)	2(4)	–(9)	–(3)	2(2)	– (7)	5(23)
500 ppm	60	37	–(2)	–(2)	–(3)	–(2)	–	2[i] (7)	2(13)
250 ppm	60	15	–	1(4)	–(2)	–(1)	–	2[j] (5)	3(9)
50 ppm	60	18	–	–	–	1[f]	–	– (3)	1(3)
No treatment	190	128	–	–	–	–	–	3[k] (3)	2(2)
Total	550	256	11(27)	3(19)	–(34)	2(12)	10(12)	17 (49)	38(117)

[a] The animals were treated by inhalation 4 hours/day, 5 days/week, for 17 weeks. ppm × 2560 = $\mu g/m^3$.

[b] Tumors found in experiment BT1 after 86 weeks are given in parentheses.

[c] Several cases of breast fibroadenomas, adrenal and pituitary tumors (generally adenomas) have not been considered, since their distribution in the different groups does not vary.

[d] Several animals with two or more tumors.

[e] One subcutaneous angiosarcoma.

[f] One orbital angiosarcoma.

[g] One parauricular fibrosarcoma; one nasal papilloma; one renal adenoma.

[h] One Zymbal gland fibroangioma; two skin carcinomas; one subcutaneous angioma; one mammary carcinoma; one forestomach papilloma; one cranial osteoma.

[i] Two lymphomas.

[j] One Zymbal gland adenoma; one retrobulbar fibroma.

[k] One Zymbal gland adenoma; two lymphomas.

Table 6.9. CARCINOGENIC ACTIVITY OF INHALED VINYL CHLORIDE IN WISTAR RATS 9 weeks FOLLOWING TERMINATION OF EXPOSURE (BT7)[6]

Treatment[a]	Number of animals (Wistar rats)		Number of animals with tumors[b]						
	Total	Survivors	Zymbal gland carcinomas	Nephroblastomas	Angiosarcomas Liver	Angiosarcomas Other sites	Brain neuroblastomas	Other type and/or site	Total
10,000 ppm	30	8	–(7)	1(3)	2(3)	–(1)	1(2)	2[c](7)	5(18)
6,000 ppm	30	13	–(1)	–(1)	–(2)	–(1)	–(1)	– (1)	–(6)
2,500 ppm	30	8	–(1)	–(1)	–(1)	–(2)	–	– (1)	–(5)
500 ppm	30	16	–(1)	–	1	–	–	–	1(1)
250 ppm	30	16	–	–	–	–	–	1[d]	1
50 ppm	30	22	–	–	–	–	–	–	–
No treatment	40	34	–	–	–	–	–	–	–
Total	220	117	–(10)	1(5)	3(6)	–(4)	1(3)	3 (9)	7(30)

[a] The animals were treated by inhalation for 4 hours/day, 5 days/week, for 52 weeks. ppm × 2560 = $\mu g/m^3$.

[b] Tumors found in male Sprague-Dawley rats of experiment BT1 after 71 weeks are given in parentheses.

[c] Two Zymbal gland adenomas.

[d] One angioma of the caecum.

Table 6.10. CARCINOGENICITY OF INHALED VINYL CHLORIDE IN SWISS MICE 9 weeks FOLLOWING EXPOSURE (BT4)[6]

Treatment[a]	Animals (Swiss mice)								
	Total			Corrected number[b]			Survivors		
	M	F	T	M	F	T	M	F	T
10,000 ppm	30	30	60	22	28	50	–	–	–
6,000 ppm	30	30	60	26	28	54	–	–	–
2,500 ppm	30	30	60	23	30	53	–	–	–
500 ppm	30	30	60	29	29	58	–	2	2
250 ppm	30	30	60	29	29	58	3	1	4
50 ppm	30	30	60	27	30	57	1	9	10
No treatment	80	70	150	74	67	141	24	34	58
Total	260	250	510	230	241	471	28	46	74

[a] The animals were treated by inhalation for 4 hours daily, 5 days weekly, for 30 weeks. ppm x 2560 = $\mu g/m^3$.

[b] Animals alive after 16 weeks, when the first tumor (a mammary carcinoma) was observed. The percentages are referred to the corrected number.

[c] Adenomas, some of which undergoing malignant transformation.

[d] In females.

[e] Several cases with two or more tumors.

[f] Four liver fibroangiomas; three subcutaneous angiomas; one heart fibroangioma; one ossifying interscapular angioma.

[g] Four liver angiomas; two liver fibroangiomas; one subcutaneous angiosarcoma; one renal fibroangioma; one thymic angioma.

[h] Three liver angiomas; three subcutaneous angiosarcomas; one subcutaneous angioma; two intra-abdominal angiosarcomas; two renal angiosarcomas; one pulmonary angioma.

[i] One liver angioma; three liver fibroangiomas; two subcutaneous angiosarcomas; one subcutaneous angioma; one subcutaneous fibroangioma; one intra-abdominal fibroangioma; three intra-abdominal angiosarcomas; one angioma of the caecum; one renal angiosarcoma; one pulmonary fibroangioma; one testicular fibroangioma.

[j] Five liver angiomas; five liver fibroangiomas; two intra-abdominal angiosarcomas; one pulmonary angioma; one scrotal angioma.

In summary, the experimental evidence indicates that vinyl chloride can act as a mutagen in microbial assay systems, can act as a transplacental carcinogenic agent, and can elicit teratogenic effects, which are potentiated by ethanol, at 500 ppm (1280 mg/m^3). Since most carcinogenic agents are mutagenic in the bioassay systems used, vinyl chloride may elicit heritable genetic effects in subsequent generations. This fact is consistent with the concerns of the Environmental Mutagen Society.[34]

The earlier reports from Maltoni and Lefemine[5] noted the use of vinyl acetate as a control in their studies of vinyl chloride. Exposure of Sprague-Dawley rats to vinyl acetate up to 2500 ppm (6400 mg/m^3) was not followed by the appearance of any tumors. A report from a group of European toxicologists discussed the relationship between the chemical structure of vinyl chloride and its toxicological effects.[35] They noted that a large number of compounds that contain double bonds may lead to free radical formation and have been shown to be carcinogenic in experimental animals. Therefore, vinyl acetate may be metabolized by a different mechanism than that of vinyl chloride.

6.1.5 Metabolism and Pharmacodynamics

Early studies indicate that vinyl chloride was not metabolized, but was absorbed, distributed throughout the body, and eliminated essentially unchanged by the pulmonary and urinary excretory routes.[12,13] These conclusions tended to support those of the earlier toxicological studies, which indicated a low order of acute toxicity for vinyl chloride. With the more recent evidence of carcinogenicity, however, more extensive investigations of the metabolism and pharmacodynamics of vinyl chloride have been initiated.[35,36]

Animals with tumors										
Pulmonary tumors[c]			Mammary carcinomas[d]			Liver angio-sarcomas, no.	Vascular tumors of other type and/or site, no.	Epithelial tumors of the skin, no.	Other type and/or site, no.	Total,[e] no.
No.	%	Average latency time, weeks	No.	%	Average latency time, weeks					
35	70	36	13	47	31	8	9[f]	3[l]	2[p]	38
38	70	38	8	28	33	5	9[g]	6[m]	4[q]	39
30	57	43	9	30	35	11	12[h]	3[n]	2[r]	31
38	66	41	7	24	37	11	16[i]	1[o]	1[s]	42
31	53	42	11	32	39	11	14[j]	–	3[t]	38
1	2	56	10	33	37	1	11[k]	–	1[u]	16
4	3	53	–	–	–	–	–	–	1[v]	5
177	–	–	58	–	–	47	71	13	14	207

[k] Two liver angiomas; two liver fibroangiomas; one subcutaneous angiosarcoma; two subcutaneous angiomas; one subcutaneous fibroangioma; one intra-abdominal angioma; one intrathoracic fibroangioma; one angioma of the interscapular fat pad.

[l] Two squamous carcinomas; one invasive acanthoma.

[m] Five squamous carcinomas; one acanthoma.

[n] One squamous carcinoma; two acanthomas.

[o] One acanthoma.

[p] One Zymbal gland adenoma; one forestomach papilloma.

[q] One lymphoma; one subcutaneous leiomyosarcoma; one forestomach papilloma; one Harderian gland adenoma.

[r] One forestomach papilloma; one parotid gland mixed tumor.

[s] One Zymbal gland adenoma.

[t] One Zymbal gland adenoma; one lymphoma; one Leydig cell tumor.

[u] One parotid gland adenocarcinoma.

[v] One lymphoma.

In 1955 von Oettingen[12] determined VC levels in the blood of cats subjected to acute exposure conditions. Exposure to 100,000 ppm (25,600 mg/m^3) for less than 4 hours produced vinyl chloride concentrations of 15 to 17 mg/100 mg blood in the animals. Respiratory arrest occurred at blood levels of VC of 27 to 30 mg/100 mg blood and cardiac arrest at levels exceeding 40 mg/100 mg blood. Approximately 82 percent of the inhaled VC was eliminated immediately from the lungs in these experiments.

The observation by Viola et al.[2,21] in 1969 using Wistar rats exposed to 10,000 ppm (2560 mg/m^3) for 60 minutes, tended to support conclusions which identify the lungs as the principal excretory route of vinyl chloride. The concentration of vinyl chloride decreased rapidly in expired air, blood, urine, brain, liver and kidneys during the first hour following exposure.[2] There was essentially no detectable level of vinyl chloride in these animals at 3 hours following exposure. Analysis of the distribution of vinyl chloride among the formed elements and the fluid media of the blood indicate red blood cells have a greater affinity for vinyl chloride than serum.

Knittle et al.[37] conducted measurements of VC in the subcutaneous fat depots of three control subjects and 11 workers exposed to the gas during the manufacture of PVC. Significant levels were found in workers exposed for periods of 5 years or more but none was found in the control group nor in two workers whose exposure history was less than 1 year. The results indicate that measurement of VC in fat stores could provide a basis for a practical screening for workers exposed to VC gas.

The metabolism and pharmacodynamics of vinyl chloride under more controlled conditions have recently been studied by Hefner et al.[35,36] A summary of the results from these studies, which involved male Sprague-Dawley rats (Spartan strain) exposed to initial concentrations of 51 to 1167 ppm (130.6 to 2997.5 mg/m^3) with exposure ranging from 52.5 to 356.3 minutes, is presented in Table 6.17.

Table 6.11. CARCINOGENICITY OF INHALED VINYL CHLORIDE IN GOLDEN HAMSTERS 18 weeks FOLLOWING EXPOSURE[6]

Treatment[a]	Number of animals (Golden hamsters)		Number of animals with tumors						
	Total	Survivors	Liver angio-sarcomas	Skin trichoepi-theliomas[b]	Melanomas	Lymphomas	Forestomach papillomas and acantho-mas	Other type and/or site	Total[c]
10,000 ppm	35	9	–	3	–	–	–	–	3
6,000 ppm	32	8	–	2	1	1	3	1[d]	5
2,500 ppm	33	11	–	1	–	–	4	–	4
500 ppm	33	13	1	1	–	1	1	1[e]	4
250 ppm	32	8	–	1	–	1	–	–	2
50 ppm	33	11	–	3	1	1	–	–	5
No treatment	70	35	–	2	–	–	–	–	2
Total	268	95	1	13	2	4	8	2	25

[a] The animals were treated by inhalation for 4 hours daily, 5 days weekly, for 30 weeks. ppm x 2560 = $\mu g/m^3$.

[b] Several cases with acanthosis and some undergoing malignant transformation.

[c] Several animals with two or more tumors.

[d] One hepatocarcinoma.

[e] One subcutaneous angioma.

Table 6.12. PRELIMINARY EXPERIMENT ON THE TRANSPLACENTAL CARCINOGENICITY OF INHALED VINYL CHLORIDE (BT5)[6]

Treatment[a]	Number of animals (Sprague-Dawley rats)		Number of animals with tumors					
			Zymbal gland carcinomas	Nephro-blastomas	Angiosarcoma		Other type and/or site	Total
	Total	Survivors			Liver	Other sites		
10,000 ppm, breeders	30	8	–	–	–	–	–	–
6,000 ppm, breeders	30	2	–	–	–	–	–	–
10,000 ppm, offspring	54	31	1	–	–	1[b]	–	2
6,000 ppm, offspring	32	15	–	–	–	1[c]	–	1
Total	146	56	1	–	–	2	–	3

[a] The breeders were treated by inhalation for 4 hours daily, from the 12th to the 18th day of pregnancy. ppm × 2560 = $\mu g/m^3$.

[b] Subcutaneous angiosarcoma on a 24-week-old male.

[c] Subcutaneous angiosarcoma on a 22-week-old female.

Table 6.13. STUDY OF ONCOGENIC ACTIVITY OF ORAL VINYL CHLORIDE[26]
(results at end of 50 weeks)

Group/treatment, mg VC/kg body weight[a]	Survivors			Angiosarcomas[b]
	Total	Female	Male	
I/50	67	34	33	1 (thymus)[c]
II/16.65	68	37	31	1 (liver)[d]
III/3.33	66	39	27	–
Control	75	39	36	–
Total	276	149	127	2

[a] A total of 320 Sprague-Dawley rats, 40 males and 40 females in each group, were treated.
[b] No tumors other than angiosarcomas were found.
[c] Female rat.
[d] Male rat. The tumor was identified at 49 weeks after onset of treatment. Lung metastasis.

Table 6.14. INTERIM SUMMARY OF TUMORS IN MICE EXPOSED TO VINYL CHLORIDE FOR 8 months[27]

Exposure group	No. of mortalities with neoplasms			Type and location of tumor			
	Total	Male	Female	Alveologenic adenomas, lung	Angio-sarcoma, liver	Adeno-squamous carcinoma, mammary gland	Metastasis of mammary tumor to lung
Control[a]	(9)	(7)	(2)	0	0	0	0
50 ppm[b,c]	4	1	3	2	2	2	2
200 ppm[b,c]	15	3	12	12	11	3	1
2500 ppm[b,c]	30	6	24	28	28	6	1

[a] Seven male and two female control mice have been examined histologically. None had tumors in spleen, liver, kidneys, heart, or lung.
[b] Only mice with grossly visible tumors have been examined histologically.
[c] ppm X 2560 = $\mu g/m^3$.

Table 6.15. TUMORS PRESENTLY CORRELATED TO VC EXPOSURE (BY INHALATION) ON EXPERIMENTAL RODENTS AND MAN[6]

Species	Tumors										
	Angiosarcomas of liver	Tumors of brain	Tumors of lung	Lymphomas and leukemias	Angiosarcomas and angiomas of other sites	Nephroblastomas	Sebaceous carcinomas	Squamous tumors of epidermis	Mammary carcinomas	Hepatomas	Forestomach papillomas and acanthomas
Rat	+	+			+	+	+	+	(+)	+	
Mouse	+				+		+	+	+		
Hamster	+		+	+	(+)			+			+
Man	+	(+)	(+)	(+)							

Table 6.16. SUMMARY AND CONCLUSIONS OF VARIOUS ASPECTS OF VINYL CHLORIDE CARCINOGENICITY DRAWN BY MALTONI AND LEFEMINE[5,6,25]

1. Under our experimental conditions, VC produced tumors in the three animals species studied: rats, mice, and hamsters.

2. The range of induced tumors varies to some extent from species to species. When given by inhalation, VC produced: in rats, Zymbal gland carcinomas, nephroblastomas, angiosarcomas and angiomas of the liver and other sites, skin carcinomas, hepatomas and brain neuroblastomas; in mice, lung adenomas, mammary carcinomas of a peculiar type, angiosarcomas and angiomas of the liver and other sites, skin epithelial tumors; in hamsters, liver angiosarcomas and, as early evidence seems to suggest, skin trichoepitheliomas, lymphomas and forestomach papillomas and acanthomas. Liver angiosarcomas have been observed in all three animal species.

3. In the BT1 and BT4 experiments, VC shows a carcinogenic effect at 50 ppm (128,000 $\mu g/m^3$).

4. From the BT1 experiment (the only one completed) a dose-response relationship clearly emerges, as far as angiosarcomas and nephroblastomas are concerned, in the lower dose ranges: i.e. from 500 to 50 ppm (1,280,000 to 128,000 $\mu g/m^3$) for angiosarcomas, and from 250 to 50 ppm (640,000 to 128,000 $\mu g/m^3$) for nephroblastomas.

5. A comparison of the results available at the present moment in rats exposed for 52 weeks and 17 weeks (BT1 and BT3 experiments) shows that the neoplastic response, particularly as far as angiosarcomas and nephroblastomas are concerned, is affected by the length of exposure to VC.

6. The comparison of the results obtained in rats of two different strains, i.e., Sprague-Dawley (BT1) and Wistar (BT7), at the present moment, seems to suggest that the strain factor considerably affects the neoplastic response.

7. The onset of two subcutaneous angiosarcomas and of one Zymbal gland carcinoma in the offspring of breeders exposed during pregnancy for 7 days appears to indicate a transplacental effect of VC.

8. Blood vessel ectasis and endothelial hyperplasia, associated or not with cellular atypia, are often observed in the liver and in other organs and tissues in treated animals, with or without angiosarcomas. Therefore, the effect of VC on blood vessels and endothelium should be considered systemic.

Table 6.17. A SUMMARY OF RESULTS OF THE METABOLISM STUDIES OF HEFNER ET AL.[35]

1. VC is quite readily metabolized to polar metabolites which are excreted predominantly in the urine of rats exposed via inhalation to an initial concentration of 50 ppm (128 mg/m^3). Smaller amounts of ^{14}C activity are excreted in the expired air as carbon dioxide and in the feces. Very little is excreted in expired air as unchanged VC.

2. A significant but small amount of ^{14}C activity is retained in tissue, particularly liver, as long as 75 hours post exposure.

3. Metabolites excreted in the urine appear to be conjugated with glutathione and/or cysteine through covalent linkage to the sulfhydryl group. This is consistent with the reduction of the nonprotein free sulfhydryl levels in the livers of exposed rats. Preliminary *in vitro* experiments[4] have shown that direct conjugation of vinyl chloride with cysteine or glutathione in aqueous solutions occurs to a small degree but very slowly.

4. Monochloroacetic acid also appears to be a urinary metabolite of VCM, when rats were exposed to 5000 ppm (12,800 mg/m^3) for an extended time.

These investigations lead the authors to speculate that a metabolic threshold for vinyl chloride may exist. The implication that there is a carcinogenic threshold, however, cannot be supported. Sprague-Dawley rats exposed to concentrations below 100 ppm (256 mg/m^3) appear to metabolize vinyl chloride fairly readily. Exposure to levels in excess of 200 ppm (512 mg/m^3) reduces metabolism considerably. This also suggests that the metabolic pathway available at vinyl chloride levels below 100 ppm (256 mg/m^3) can be saturated. The fact that a pathway may be saturated above a given concentration does not mean that below that saturation concentration alternative metabolic pathways are inoperative. These investigators further conclude that vinyl chloride appears to be metabolized by alcohol dehydrogenase since it can be inhibited by pyrazole (1,2-pyrazole), and ethanol. The metabolism of vinyl chloride did not appear to be inhibited by SKF-525-A, a drug used to block the activity of some microsomal enzymes (mixed function oxidases) which are important in steroid metabolism and detoxification of biologically foreign chemical compounds. Metabolism by the mixed functional oxidase system is suggested when the alcohol dehydrogenase pathway was saturated somewhere above 200 ppm (512 mg/m^3). While these are preliminary conclusions, they suggest that a carcinogenic epoxide metabolite would not be formed by the alcohol dehydrogenase pathway. Attempts to infer a carcinogenic threshold for man are not justified. Such attempts would not adequately consider the genetic variation that exists among the heterogeneous human population compared to the genetic homogenicity of experimental animals. It also assumes that the alcohol dehydrogenase pathway is open and can accommodate vinyl chloride metabolism at each instant and each exposure. It would also have to accommodate the host of other foreign compounds, nutrients, etc., that are continually passing through the pathway. Public health considerations would also involve those very young and aged individuals who have little or no activity of the alcohol dehydrogenase enzymes and mixed function oxidases. Experimental evidence of transplacental carcinogenicity tends to support this concern. Furthermore, these investigators noted that vinyl chloride is excreted largely in the urine as B-hydroxy-cysteine that is in itself suggestive of metabolic transformation by an epoxide intermediate. The elimination of foreign compounds by the formation of an epoxide intermediate followed by conjugation with thiol-containing compounds is common to the metabolism of a number of chemical carcinogens.

P.L. Grover, P. Sims, and their coworkers have tested a number of carcinogens for *in vivo* and *in vitro* formation of epoxides, which have been shown to be alkylating agents of nucleic acids and proteins.[35,41] They have presented evidence for formation of epoxides for a number of carcinogens including pyrene, benzo[a]pyrene, phenanthrene, benz[a]anthracene and dibenz[a,h]anthracene. Epoxides of polycyclic hydrocarbons have been shown to be mutagenic to T_2 bacteriophage, to bacteria, to *Drosophila sp.* and to mammalian cells. They also produce malignant transformations of cells in culture.[42]

Recent studies conducted by Reynolds et al.[15] indicate the potentiation of vinyl chloride toxicity by agents that induce the activity of the detoxifying mixed-function oxidase enzymes. These studies have obvious public health considerations since these inducing agents were drugs and pollutants such as polychlorinated biphenyls and pesticides. Individuals exposed to these agents as well as alcohol appear to be at greater risk to liver damage through exposure to vinyl chloride than those who are not. Postulated metabolic mechanisms of carcinogenicity of VC and structurally related compounds have been reviewed by van Duuren[38] and investigated by Reynolds et al.[15]

6.1.6 Toxicity of Polyvinyl Chloride

The free radical content and the level of residual VC in PVC resins and plastic end products could affect their toxicity and their potential for carcinogenic activity. Volkheimer[43] reported that PVC particles up to 70 micrometers in diameter could be transported and deposited throughout the tissues of experimental animals.

Another potential problem area related to vinyl chloride is the composition and toxicity of products produced by incineration of PVC. Again, this is a potentially widespread opportunity for general population exposure to other hazardous materials. Disposal of PVC by incineration is a common practice, and incomplete combustion can result in releasing entrapped vinyl chloride and plasticizers, in addition to combustion products (HC1).[44]

Sokal et al.[45] reported respiratory symptoms in workers, employed as meat wrappers, exposed to fumes from polyvinyl chloride film cut with a hot wire. Symptoms included dyspnea, coughing, and wheezing. Tests of pulmonary function generally showed obstructive defects with decreased vital capacity and increased residual lung volume responsive to bronchodilator therapy. The cause of the symptoms was not definitely established; however, the authors suspected some ingredient of the fume from the heated polyvinyl chloride.

Jaeger and Hites[46] conducted a study to determine whether di-2-ethyhydroxyl adipate (DEHA), a plasticizer used in PVC plastic food wrap, would pyrolytically evaporate when the film was heated. The results did show DEHA to be a pyrolysis product from PVC film when heated at temperatures from 275 to 350°F.

Van Hauten et al.[47] found that the concentration of hydrochloric acid and particulate produced by a typical meat wrapping machine, using polyvinyl chloride film, varied significantly with wire temperature and operating conditions. Approximately 75 percent of the particulate produced by the machine was found to be DEHA.

In a study conducted by the University of Michigan, vinyl chloride was found to be a pyrolysis product from PVC plastics at combustion temperature below about 500°C.

6.2 THRESHOLD LIMIT VALUES

Although occupational health studies associated with polyvinyl chloride production and/or exposure to vinyl chloride monomer began in 1930, there were essentially no reports of possible systemic effects or serious health adversities until 1949. Chronic "epithelial" hepatitis was diagnosed in Russian resin fabricators engaged in processing PVC resins.[11] The possible etiological agents listed included primary ingredients used for polymerization, compounds released from the resin during processing, and plasticizers.

A threshold limit value (TLV) of 500 ppm (1280 mg/m^3) time-weighted average was established in 1959 by the American Conference of Governmental Industrial Hygienists (ACGIH) as the industrial hygiene standard for VC in the United States This standard apparently was based solely upon the fire and explosive hazards that are possible at a minimal level of 2.5 percent (25,000 ppm or 64,000 mg/m^3) by weight of VC in air.

The results of acute toxicity studies provided evidence of pulmonary congestion (edema), with damage noted in the liver, kidneys, and tracheal epithelium, as well as narcotic effects associated with high exposure levels of short duration. The evidence of organ damage and/or systemic effects observed under acute exposure conditions, led to the chronic (low level) inhalation studies of Torkelson et al.[17] in 1961. Based on observations in several species of experimental animals that included evidence of liver and kidney pathology at the TLV (500 ppm or 1,280,000 $\mu g/m^3$), and the absence of these effects at 50 ppm (128,000 $\mu g/m^3$) following 6 months of investigation, these authors recommended a change in the industrial hygiene standard. They suggested limiting occupational vinyl chloride exposures to less than 100 ppm (256,000 $\mu g/m^3$) with a time-weighted average not to exceed 50 ppm (128,000 $\mu g/m^3$) in air of the PVC workroom.

The ACGIH's Committee on the Threshold Limit Values therefore changed the industrial hygiene standard for VC from a 500-ppm maximum time-weighted average (TWA) value to a 500-ppm (1,280,000-$\mu g/m^3$) ceiling level.

Vinyl chloride disease, or acroosteolysis, was first reported in 1966.[11] This disease involved a progressive skeletal deterioration of the fingers accompanied by interference in peripheral nerve response and diminished blood circulation (Raynaud-like syndrome). While other reports have appeared in subsequent years, occupational acroosteolysis in PVC reactor cleaners has been well documented by large scale epidemiological studies conducted between 1969 and 1972. [1,11] Prior to 1970, available standard textbooks and review articles have stressed the safety of polymer processing and noted only a minimal risk of narcosis associated with inhalation of VC.[48-51]

The studies on occupational exposure to VC that were influential in adjusting permissible exposure levels were those of Baretta et al.[52] and Kramer and Mutchler.[53] (The study by Kramer and Mutchler is discussed in more detail in Section 6.3.3.) These investigations involved determining levels of vinyl chloride in the air of the work area and correlating them with results of a systematic screening of employees using a variety of clinical parameters. The mean concentration of vinyl chloride in the work environment in these studies was found to be 160 ppm (409,600 $\mu g/m^3$) with a range of 30 to 170 ppm (76,800 to 435,200 $\mu g/m^3$). Vinylidine chloride at a level of 5 ppm (12,800 $\mu g/m^3$) was noted as a co-contaminant. No differences were observed in blood pressure, hemoglobin levels, or electrocardiograms; nor was there evidence of morphological anomalies (acroosteolysis). Still, there was indication of some degree of liver damage among PVC employees at time-weighted average (TWA) exposures of 300 ppm (768,000 $\mu g/m^3$). These observations led the investigators to conclude that there was a definite risk of liver damage at vinyl chloride levels of 300 ppm (768,000 $\mu g/m^3$) TWA in the presence of 5 ppm (12,800 $\mu g/m^3$) of vinylidine chloride.[53]

An adjustment of the industrial hygiene standard to a TLV of 200 ppm (512,000 $\mu g/m^3$) in 1972 was apparently influenced by evidence of human liver dysfunction, and the availability of monitoring data from at least one PVC production facility.[52-54]

Due to the increasing incidence and concern regarding acroosteolysis, Viola, in 1970 and 1971, undertook experimental studies to develop an animal model to explain this and other adverse effects observed in humans exposed to high levels of vinyl chloride.[21,22] In the course of these acute studies, carcinogenic effects were observed. The observations were presented in 1970, followed by a detailed publication in 1971. Although the experimental design was deficient with regard to carcinogenic investigations, the evidence warranted further study. Subsequent investigations were initiated in Europe and in the United States, using lower exposure levels and purer compounds.[5-7] Preliminary results from these efforts confirmed the carcinogenicity of vinyl chloride in several species of experimental animals; a dose-response dependency of total tumor incidence was observed; and positive effects were detected at exposure levels down to 250 ppm (640,000 $\mu g/m^3$).[4,5]

Due to the history of liver dysfunction in PVC employees and in the chronic experimental animal studies observed earlier, particular concern was aroused by the appearance of angiosarcoma, rare in experimental animals and man, in the same critical organ, the liver.[4,5] Concern with respect to VC followed the findings that from 1968 to 1973 four employees at a PVC plant had died of either liver angiosarcoma or other liver cancers of unknown type.[8] A fifth individual in the same plant died in late 1973 of cirrhosis of the liver. Investigation of the exposure history of these individuals revealed that the deceased employees had an average exposure period of 19 years to VC, and 10 years to vinylidine chloride. These workers had been engaged in operations where VC concentrations may have greatly exceeded the 1972 TLV of 200 ppm (512,000 $\mu g/m^3$).

The Occupational Safety and Health Agency (OSHA) in January 1974 set an emergency standard for industrial exposure at 50 ppm (128,000 $\mu g/m^3$).[55] Results from the American and European chronic studies soon revealed the induction of liver angiosarcoma and other tumors at a 50 ppm (128,000 $\mu g/m^3$) exposure level of vinyl chloride.[4,5,7] Industrial epidemiological investigations identified additional cases of liver angiosarcoma among American and European PVC workers. An occupational standard of 1.0 ppm (2560 $\mu g/m^3$) (or detectable levels) was then proposed by OSHA.[56] Subsequently, a permanent 1 ppm (2560 $\mu g/m^3$) TWA occupational standard (8 hours per day; 5 days per week), with a peak 15 minute excursion not to exceed 5 ppm (12,800 $\mu g/m^3$), was promulgated in May 1974.

The incidence of angiosarcoma among employees involved in the manufacture of VC and PVC resins substantially exceeds the estimated national incidence level, as discussed in Section 5. Interest has been expressed regarding possible community exposures among those whose residences are situated near VC/PVC production plants and resin fabricating facilities. There is similar concern with respect to possible community exposure surrounding fabricating plants using PVC resins containing residual VC. Vinyl chloride has been detected in the ambient air near vinyl chloride and polyvinyl chloride production sites.

6.3 HUMAN EFFECTS

Our knowledge of undesirable effects associated with vinyl chloride exposure in man comes primarily from occupational situations. These effects include an increased risk of cancer of multiple organ sites including angiosarcoma of the liver. Angiosarcoma of the liver, observed today in workers exposed to VC, probably was the result of very high occupational exposures received many years ago. The latent period for angiosarcoma of the liver has been estimated at 15 to 20 years following onset of exposure.[57,58] A long latency period is an integral part of the natural history of the disease; therefore, the full impact from past vinyl chloride exposure among workers may not be realized until many years from now since the greatest number of workers have had onset of exposure in the last decade. For example, of the confirmed cases of liver angiosarcoma, information as to date of diagnosis or death, where available, indicates that only 2 of 27 cases died prior to 1965 and that 15 of 27 cases had died or were diagnosed in 1970 or later.[58] A "confirmed" case has been microscopically confirmed, whereas a "reported" case is reported merely on the results of a pathologic examination. Accordingly, estimates of cancer risk from vinyl chloride, based upon data available today, may well understate the magnitude of this problem. In this regard, increased awareness and improved diagnostic procedures may in part also contribute to future increases in reported cases of liver angiosarcoma.

6.3.1 Confirmed Cases of Angiosarcoma

To date, surveys have reported 17 occupational cases of liver angiosarcoma in the U.S.A.;[58,59] of these cases 15 have been confirmed as angiosarcoma of the liver by pathologists at the National Cancer Institute.[60] Of these confirmed cases, 14 have been among workers in PVC polymerization plants, and one of the confirmed cases involved an accountant employed at a vinyl cloth plant. The accountant is presumed to have had a lower level of exposure than the PVC workers. In addition to these U.S. cases, 21 occupational cases of liver angiosarcoma have been reported from European countries and Canada, 12 of which have been confirmed microscopically (Table 6.18). Nine of the confirmed cases were among workers in the PVC polymerization industry and 3 were among nonpolymerization workers. A summary of these reported occupational liver angiosarcoma cases is shown in Table 6.18.

The period from onset of initial exposure to diagnosis or death is 10 years or greater in all known instances. Similarly, the years of exposure among these individuals preceding development of clinical disease is, with two exceptions, in excess of 10 years.[58]

With respect to the general population, cases of liver angiosarcoma were reported among individuals who had resided in the vicinity of industrial vinyl chloride emission sources. A review of these cases by pathologists at the National Cancer Institute has confirmed the diagnosis of liver angiosarcoma in two of the three instances. One case of a woman in Buffalo, New York, that was originally believed to be liver angiosarcoma[61] has now been rediagnosed as anaplastic carcinoma rather than a sarcoma.[62] The two other cases, both from Connecticut, represent confirmed angiosarcoma,[62,63,25] but these cases are not identical in all respects to the pathology which has been observed among PVC polymerization workers [60,25,64] (see Table 6.19). The implications of these dissimilarities between community and occupational cases are not fully understood.

6.3.2 Reported Studies

As a result of the reported cases of liver angiosarcoma among vinyl chloride workers, a number of studies have compared the mortality experience of these workers to that of the general population.

6.3.2.1 *Tabershaw/Cooper Study*–Tabershaw/Cooper Associates conducted a mortality study of workers in the vinyl chloride industry.[64,9] The objectives of this study were threefold: (1) to contrast the mortality experience of individuals employed in vinyl chloride plants with that of the general population, (2) to examine mortality patterns among vinyl chloride workers in relation to estimated occupational exposure, and (3) to compare mortality patterns among vinyl chloride workers with those for other occupational groups.

Table 6.18. REPORTED CASES OF LIVER ANGIOSARCOMA AMONG PVC WORKERS AND NON-PVC WORKERS[58,a]

Country	Case No.	Birth date	First VC or PVC exposure	Angiosarcoma diagnosed (DX)	Age at DX	Yr from 1st exp. to DX	Total yr exp.	Date of death
Canada	01[b]							
Canada	02[b]							
Canada	03[b]							
Canada	04[b]							
Czechoslovakia	01[b]							
Czechoslovakia	02[b]							
France	01[c]	00-00-00	00-00-00	00-00-00	43	19	19	00-00-67
Great Britain	01[c]	00-00-01	00-00-46	12-00-72	71	26	20	12-00-72
Great Britain	03	06-00-37	02-00-66	00-00-74	38	8	4	12-24-74
Italy	02[c]	11-13-29	00-00-57	12-13-72	43	15	6	12-00-72
Norway	01[c]	12-23-16	03-00-50	12-20-71	56	22	21	01-04-72
Rumania	01[b]							
Sweden	01[c]	06-23-27	08-14-51	02-00-70	43	19	18	10-20-70
United States	01[c]	10-17-23	12-09-43	03-03-73	49	22	16	03-03-73
United States	02[c]	08-19-33	11-15-56	06-00-70	36	14	13	09-28-71
United States	03[c]	05-25-15	11-28-45	12-19-73	58	28	28	12-19-73
United States	04[c]	01-15-24	07-06-52	08-19-67	43	15	15	01-07-68
United States	05[c]	01-25-12	06-19-44	04-09-64	52	20	18	04-09-64
United States	06[c]	00-00-29	01-17-62	02-00-74	45	12	12	Alive
United States	07[c]	05-03-22	08-00-44	00-00-68	45	24	18	03-23-68
United States	08[c]	05-06-20	10-07-46	08-00-61	41	15	15	08-29-61
United States	09[c]	11-08-31	09-09-54	03-01-74	43	17	17	Alive
United States	10[c]	08-16-13	06-12-51	06-00-68	56	17	17	05-10-68
United States	11[c]	06-27-08	10-14-46	03-00-70	61	23	23	03-16-70
United States	12[c]	11-17-18	09-13-40	05-02-69	50	20	15	05-02-69
United States	13[c]	12-01-21	08-19-44	05-00-74	53	30	30	07-04-74
United States	16[c]	11-04-27	06-08-50	00-00-69	41	17	4	03-27-69
United States	17	05-08-31	08-23-55	10-11-74	43	19	19	Alive
W. Germany	01[c]	07-26-31	10-14-57	09-25-70	40	11	11	12-14-71
W. Germany	02[c]	06-24-30	10-01-57	09-19-68	38	13	13	01-25-69
W. Germany	04[c]	00-00-00	00-00-00	00-00-00	44	17	11	00-00-00
W. Germany	06[c]	00-00-00	00-00-00	00-00-00	49	11	11	Alive
Great Britain	02[c,d]	09-08-14	00-00-46	02-00-70	55	24	11	12-00-70
Italy	01[e,f]	06-15-34	00-00-65	04-19-71	36	6	3	04-16-71
Sweden	02[c,g]	11-27-11	00-00-45	06-15-72	61	27	23	08-16-72
United States	14[h,i]	00-00-13	08-18-38	06-00-73	60	36	30	07-03-73
United States	15[c,j]	00-00-25	00-00-00	07-00-72	47	00	00	02-15-73
W. Germany	03[c,k]	07-16-30	00-00-00	02-00-68	43	14	14	10-10-73

[a] 00 indicates unknown data.

[b] Awaiting details.

[c] Microscopically confirmed angiosarcoma of the liver.

[d] Pouring PVC oil mixture onto fabric bases.

[e] Production of PVC sacks.

[f] Angiosarcoma involving liver, lung, and pericardium. Although difficult to determine, primary site seems to be pericardium.

[g] Production of vinyl chloride.

[h] Machine operator covering electrical wire with PVC plastic insulation.

[i] Diagnosis: sarcoma (possibly "angiosarcoma"), liver. Possibility of generalized neoplasm of the reticuloendothelial cell system cannot be ruled out.

[j] Accountant at plant making PVC fabric.

[k] Loading pesticide cans with VC propellant.

Table 6.19. HISTORICAL DATA, CASES OF HEPATIC ANGIOSARCOMA, CONNECTICUT, 1935-1973[63]

No.[a]	Age	Sex	NCI diagnosis	Date of original diagnosis	Date of death	Medical history	Laboratory data	Occupation	Place of residence
1	76	F	Hepatic angiosarcoma	3-12-50	3-19-50	1-month history of anorexia with abdominal pain and back pain. Firm epigastric mass. Died 6 days after admission with carcinomatosis and pulmonary emboli.	Alk phos 11.5 U Pro time WNL Bili 0.9 mg% X-ray: enlarged liver	Housewife	Windsor Locks
2	69	M	Carcinoma of pancreas			(Excluded from series)			
3	58	F	Carcinoid bronchoadenoma			(Excluded from series)			
4	73	M	Hepatic angiosarcoma, alcoholic cirrhosis	11-25-67	12-3-67	2-month history of diarrhea, anorexia, and 20-lb weight loss. Intermittent abdominal pain. Nontender, firm epigastric mass. Died after 9 days with spontaneous ruptured liver leading to shock. Past history of alcohol intake.	Bili 1.5/0.9 mg% Alk phos 3.0 U, LDH 500 U SGOT 64 U, SGPT 26 U Pro time 14.0 sec/11.0 control Total protein 6.7/alb 3.7 mg% Liver scan: mass behind liver	Fireman 1917-42 Aluminum worker 1942-44 Corset cutter 1945-61 Retired 1961-67	Bridgeport–entire life
5	47	M	Hepatic angiosarcoma, portal fibrosis	1-15-73	2-15-73	Initial symptom RUQ abdominal pain with vomiting. Cecal volvulus found, Rx cecopexy, over next 6 weeks pain continued with weakness. RUQ tenderness with 2 FB liver. Diagnosed by needle biopsy on 1-15-73. Deteriorated slowly until death 31 days later.	Bili 0.5/0.3 mg% Alk phos 342 U, LDH 137 U,SGOT 50 U TP 7.1/alb 2.9 mg% Scan: multiple filling defects in liver Celiac angiogram: multiple avascular masses in liver.	Accountant–vinyl co., 1963-73 Accountant–plastic belt co., 1956-63 Previously accountant other states	Bridgeport–1956-73,previously many locations

6	61	M	Hepatic angiosarcoma	6-15-73	7-3-73	6 weeks of pain, first in R shoulder, later R hip and leg. 1 week of low back pain and weakness. 10-cm nontender, sharp liver. Diagnosed by needle biopsy. Slow deterioration to death 19 days later	Bili 1.1/0.6 mg% Alk phos 307 U (had bone metastasis) LDH 241 U SGOT 46 U, SGPT 13 U TP 8.6 mg%/alb 3.4 5' nucleotidase 15.5 IU (N=3.2-11.6 IU) α-1-fetoprotein-negative	Electrical products plant, 1933-71; worked there with PVC 1938-63 Retired 1971-73 Also special policeman	Fairfield
7	50	M	Hepatic angiosarcoma	--	5-4-73	Admitted for abdominal pain and jaundice 3-27-73. 4 FB liver. Discharged. Readmitted 4-29-73 with abd distension, general edema, icterus, fever, shaking chills. Rapid downhill course with death due to renal and hepatic failure. Past history of alcohol intake.	Bili 8.3/5.8 mg% Alk phos 235 U, LDH 340 U SCOT 130 U, SGPT 49 U TP 6.1 mg%/alb 2.0 α-fetoprotein-negative	Fisherman and carpenter before 1959 Plasterer 1959-60 Unemployed 1960-73	Puerto Rico 1923-59, New York City 1959-73, Bridgeport 1973
8	83	F	Hepatic angiosarcoma	12-19-73	1-22-74	Admitted 12-2-73 with short history of RUQ abdominal pain radiating to R shoulder. Had RUQ tenderness. Open liver biopsy 12-19-73 showed large tumor. No resection. Deteriorated until death 34 days later.	Bili 0.9/0.5 mg% Alk phos 87 U, LDH 334 U SGOT 25 U, SGPT 7 U TP 7.2 mg%/alb 3.4 Urine urobilinogen 2.6 mg/2 hr (N=1.2 mg/2 hr)	Housewife Restaurant cook 35 years	Stratford 35 years

[a] Original number series from Connecticut Tumor Registry. See notes on cases listed by number.

Table 6.19 (Continued).–HISTORICAL DATA, CASES OF HEPATIC ANGIOSARCOMA, CONNECTICUT, 1935-1973[63]

1. The angiosarcoma of the liver of this patient is believed to be different from most of the angiosarcoma seen in VC-PVC workers. Sinusoidal dilatation and/or megalocytosis of hepatocytes were not seen. Also there was no hepatic fibrosis similar to that seen in the VC-PVC workers.

2. Carcinoma involving pancreas and liver, possibly primary in the pancreas. A carcinoma of this type is not present among the known VC-PVC workers whose lesions have been reviewed.

3. The carcinoid type bronchial adenoma seen in the lung of this patient almost surely has no relationship to the hepatic lesions (hemangiomas) in the liver. No bronchial adenomas have been observed in the VC-PVC workers examined.

4. The angiosarcoma in this patient forms capillary slit-like spaces and replaces hepatic tissues. This type of histological pattern is found only occasionally in the angiosarcomas of the VC-PVC workers and,in those patients,always involved multicentric areas of angiosarcomas with sinusoidal and/or capillary pattern. These types of patterns are not observed in this patient; thus, his hepatic angiosarcoma is not thought to be characteristic of the angiosarcomas seen in VC-PVC workers. Also, this patient's liver is definitely cirrhotic with large deposits of iron. These features were not seen in the VC-PVC workers with hepatic fibroses and with or without hepatic angiosarcomas.

5. The diagnosis on this case is uncertain. One histological feature, i.e., the cells of the angiosarcoma are somewhat "fibroblastic", is dissimilar to angiosarcomas seen in most VC-PVC workers. However several other histological features are similar to the VC-PVC workers' hepatic lesions, namely sinusoidal dilatation, sectorial and enveloping features of the sinusoidal lining cells, portal tract fibrosis, and variability in size of hepatocytes. There are sufficient histological similarities that prevent this case from being excluded as a so-called "VC-PVC type case."

6. It is uncertain whether this is an angiosarcoma of the liver or even a primary sarcoma of the liver. It is not like any of the other tumors seen in the livers of VC-PVC workers.

7. The histological features of the hepatic angiosarcoma and portal tract fibrosis seen in this case are similar in nearly all respects to the lesions we have seen in most of the VC-PVC workers' livers.

8. Only needle biopsies have been reviewed from this patient's angiosarcoma. The amount of material is insufficient for a definite comparative statement, but histological features,which are believed most characteristic of the angiosarcomas in VC-PVC workers, are not seen.

The study population—from 33 domestic plants—was composed of 8384 individuals with at least 1 year of occupational exposure to VC. The study population included retired and terminated as well as currently employed workers. The vital status of these workers was ascertained as of December 31, 1972, and cause of death was determined based upon available death certificates. Observed mortality was then compared to expected mortality based upon the United States male population, taking into account age and time of death. Standardized mortality ratios were computed for total mortality and specific causes of death.

Exposure categories were defined subjectively by industrial hygiene and safety personnel at each plant. They identified those jobs and work locations with the highest exposures to VC, then classified other job categories accordingly as medium or low. This procedure was reasonable for estimating relative exposure within a given plant. However, it could not assure comparable exposure categories across all plants or over time, since a low exposure in past years might be numerically equivalent to a relatively high exposure in recent years. An exposure index was calculated for each worker as a time-weighted average of exposure categories over the period of employment, thus defining two overall exposures, low and a high.

Followup procedures were able to define the vital status for 7128 workers (85 percent of the study population) as of December 31, 1972. Among the 352 workers known to have died, death certificates were obtained for 328. The mortality calculations considered only those workers who had been traced, which assumes that the mortality experience of these workers was equivalent to that of workers not traced. The median birth year for those traced was 1931 compared to 1920 for those not traced. The median year in which exposure began was 1962 among those traced compared to 1953 among those not traced. The median duration of employment for those followed was 80 months in contrast to 44 months for those who were not traced. Thus, while those traced had worked about twice as long as those not traced, their employment began about 10 years later. Accordingly, the mortality experience among those not traced might have been different from that in the study population considering the increased latent period. About 60 percent of the study population entered employment in 1960 or later, indicating that the majority of workers in this study could not be followed long enough to assure observation of all potential long-term effects. Included among the 7128 workers traced, however, were 854 workers with exposure of 20 or more years and 1640 workers with exposures of 15 years or more.

After examining the effects of exposure index (low versus high), and duration of exposure (less than or greater than 5 years) upon mortality, as well as interaction effects between level and duration of exposure, the following observations were made in the Tabershaw/Cooper study:

- Compared to the general male U.S. population, the overall mortality of the study population was approximately 75 percent of what would have been expected. (Note - this favorable overall mortality frequently occurs in occupational groups—even if an industrial hazard increases the risk of death from a particular cause—since occupational groups are usually healthier than the average population.)

- Increases in specific cause of death over the expected occurrence in the U.S. male population were not statistically significant.

- No deaths identified as angiosarcomas of the liver were found other than those previously identified.

Standardized mortality ratios (SMR) for malignant neoplasms as a whole increased with increasing exposures as measured by level, duration, or both (see Table 6.20). For example, 36 malignancies were observed in the high exposure group with 5 years or more exposure compared to 26 expected cases. Among those with greatest exposure, cancers of the liver (primarily angiosarcoma), respiratory system, and brain; cancers of unknown primary site; and lymphosarcoma occurred more frequently than expected. These findings were not statistically significant. However, the authors of the Tabershaw/Cooper study considered them suggestive of a relationship between exposure to vinyl chloride and increased cancer risk at multiple sites.

Table 6.20. OBSERVED DEATHS/EXPECTED DEATHS AND STANDARDIZED MORTALITY RATIOS IN VC WORKERS WITH EXPOSURE INDICES OF 1.5 OR GREATER, BY DURATION OF EXPOSED EMPLOYMENT[64]

Cause of death with I.C.D. No.	<60 months exposure		≥60 months exposure	
	Obs/exp	SMR[a]	Obs/exp	SMR[a]
All causes	38/47.93	79	119/147.81	81[b]
Tuberculosis (001-019)	0/0.76	0	0/1.57	0
Tuberculosis of respiratory system (001-008)	0/0.71	0	0/1.48	0
Malignant neoplasms (140-205)	5/6.57	95	36/26.11	141
Malignant neoplasms, buccal cavity and pharynx (140-148)	0/0.23	0	0/0.99	0
Malignant neoplasms, digestive organs and peritoneum (150-159)	1/1.67	76	11/7.47	151
Malignant neoplasms, respiratory system (160-164)	1/1.79	71	12/8.50	144

Table 6.20 (continued). OBSERVED DEATHS/EXPECTED DEATHS AND STANDARDIZED MORTALITY RATIOS IN VC WORKERS WITH EXPOSURE INDICES OF 1.5 OR GREATER, BY DURATION OF EXPOSED EMPLOYMENT[64]

Cause of death with I.C.D. No.	<60 months exposure		>60 months exposure	
	Obs/exp	SMR[a]	Obs/exp	SMR[a]
Malignant neoplasms, genital organs (170-179)	0/0.29	0	1/1.41	73
Malignant neoplasms, urinary organs (180-181)	0/0.26	0	0/1.26	0
Malignant neoplasms, other and unspecified sites (190-199)	1/1.18	107	7/3.51	204
Leukemia and aleukemia (204)	1/0.44	288	1/1.13	90
Lymphomas (200-203, 205)	1/0.71	178	4/1.84	222
Diabetes mellitus (260)	0/0.61	0	2/2.04	100
Major cardiovascular and renal diseases (330-334, 400-468, 592-594)	7/16.54	54[c]	62/70.46	90
Vascular lesions affecting CNS (330-334)	2/1.87	135	4/8.19	50
Rheumatic fever and chronic rheumatic heart dis. (400-402, 410-416)	0/0.82	0	2/2.04	100
Arteriosclerotic heart disease (420)	5/10.41	61[a]	46/47.65	98
Nonrheumatic endocarditis (421, 422)	0/0.57	0	1/2.32	44
Hypertensive heart disease (440-443)	0/0.76	0	2/3.10	66
Other hypertensive disease (444-447)	0/0.27	0	2/0.81	253
Chronic and unspecified nephritis and renal sclerosis (592-594)	0/0.54	0	0/1.23	0
Influenza and pneumonia (480-493)	0/0.99	0	0/3.13	0
Ulcer of stomach and duodenum (540, 541)	1/0.35	362	0/1.25	0
Appendicitis (550-553)	0/0.08	0	0/0.9	0
Hernia and intestinal obstruction (560, 561, 570)	0/0.14	0	1/0.49	209
Gastritis, duodenitis, enteritis and colitis (543, 571, 572)	1/0.14	904	0/0.41	0
Cirrhosis of liver (581)	0/1.56	0	1/5.08	20
Hyperplasia of prostate (610)	0/0.01	0	0/0.13	0
Symptoms, senility and ill-defined conditions (780-795)	1/0.80	158	0/2.30	0
All other diseases (residual)	0/4.02	0	6/11.88	51[a]
Motor vehicle accidents (810-835)	7/6.05	146	2/7.43	28
Other accidents (800-802, 840-952)	4/4.73	107	2/7.96	26
Suicide (963, 970-979)	3/2.40	158	4/4.62	88
Homicide (954, 980-985)	1/2.18	58	0/2.76	0
No. of workers	1240		1817	
Person-years	12,828		19,305	

[a] Standardized mortality ratios adjusted for deaths with cause unknown.

[b] Significant at 5 percent level.

[c] Significant at 1 percent level.

6.3.2.2 *Dow Chemical Study* Dow Chemical conducted a long-term mortality study of 594 chemical workers exposed to vinyl chloride between the years 1942-1960.[65,66] The study population was defined as production workers at one manufacturing facility who worked in areas with potential vinyl chloride exposure. Each job classification was assigned an exposure rating of low, intermediate, or high, depending on existing industrial hygiene data. This was the only available mortality study in which VC exposures could be reconstructed using relative degrees of exposure. Three categories of exposure were defined based upon estimated time-weighted average (TWA) concentrations for an 8-hour day:

- Low exposure group, TWA below 25 ppm VC (964,000 $\mu g/m^3$).
- Intermediate exposure group, TWA ranging from 25 to 200 ppm (64,000 to 512,000 $\mu g/m^3$).
- High exposure group, TWA of 200 to 300 ppm (512,000 to 768,000 $\mu g/m^3$). Also included in the high group were those with TWA exposures in the intermediate range but also exposed to frequently unpredictable excursions above 1000 ppm (2,560,000 $\mu g/m^3$).
- A fourth category of indeterminate exposure was defined for individuals working in areas where sufficient air monitoring data were not available.

Assignment to exposure groups was determined by the highest exposure experience for one or more months. By this procedure, the lowest exposure category contained only individuals with low exposure whereas the highest exposure group included some individuals with predominantly lower exposures. Durations of exposure were categorized as less than 1 year and 1 year or longer. (Note: effects of exposure well above 1 year were not adequately examined, although the analysis did consider the impact of latency period.) Of the 594 employees in this study, 72 had histories of exposure to both VC and arsenicals. In view of the cancer risk associated with arsenicals, the 72 with arsenic exposure were excluded from dose-response relationships related to VC.

Expected deaths in this cohort were determined from U.S. white male mortality rates. Death certificates were obtained for 86 of the 88 individuals known to be dead. Of the 148 individuals who had left the company, 131 were traced. Among the individuals who had worked with arsenicals and VC, 7 of 10 deaths were due to neoplasms, compared to 1.9 cancer deaths expected; 3 lung cancers were noted in this group. Among workers exposed to VC, but not arsenicals, observed deaths were 91 percent of the expected deaths based upon the U.S. white male population. No deaths due to angiosarcoma of the liver or other liver cancers were noted in the group exposed to VC but not arsenicals. For this group as a whole, total malignancies were only 13 observed, compared to 15.4 expected.

The effects of exposure grouping upon malignancy rate were examined for this cohort exclusive of arsenical workers. Of 163 individuals in the high-exposure group, 27 had 20 or more years at low to high exposure and only 19 had 10 or more years of only high exposure. Of the 13 malignancies observed in this cohort, 9 occurred in the high-exposure group, compared to 5.1 expected. Due to the small number of deaths involved, this difference was not tested for statistical significance. To examine for possible latent effects, the mortality experience of workers with 15 or more years since onset of exposure was studied. In this group, nine malignancies were observed, eight in the high-exposure group. Accordingly, eight of the nine malignancies observed in the high-exposure group occurred 15 or more years after onset of exposure. Table 6.21 summarizes the results.

The authors of the Dow Chemical Study concluded that workers exposed to VC at levels above 200 ppm (512,000 $\mu g/m^3$) experienced an "apparent increase in overall malignancy rate." When exposures were kept below 200 ppm (512,000 $\mu g/m^3$) the malignancy rate decreased. Angiosarcomas of the liver were not found at any level of exposure. Among the workers exposed above 200 ppm (512,000 $\mu g/m^3$) TWA, the increase in overall malignancy was not statistically significant. The authors also commented as to possible cocarcinogenic effects of other exposures with VC, particularly benzene, cigarette smoking, and arsenic.

Table 6.21. SUMMARY OF DOW MORTALITY STUDY[65,a]

Category	Observed mortality	Expected mortality	Standardized mortality ratio (SMR)
All causes	78	85.7	91
All cancers			
All VC exposed	13	15.4	84
Only high exposure group	9	5.1	176
< 1-yr exposure	3	2.2	136
≥ 1-yr exposure	6	2.9	209
High exposure group with			
15 yr after onset of exposure	8	3.2	250
< 1-yr exposure	3	1.3	231
≥ 1-yr exposure	5	1.9	263

[a] Study population: (1) excluded workers exposed to arsenicals; (2) years exposed—1 or more; (3) onset since first exposure—no restriction; (4) size of cohort—594 total, 522 with VC exposure only; (5) number successfully followed up—577.

In reviewing these data, certain strengths in this study are evident, especially the availability of measured vinyl chloride exposures and the successful followup of over 95 percent of the whole. However, there are also several weaknesses. The level and duration of exposure to vinyl chloride is widely variable among individuals within the high exposure group. Since only 1 month of exposure to levels of 200 to 300 ppm (512,000 to 768,000 $\mu g/m^3$) TWA was required to place an individual in the high exposure group, only 9 of the 163 men in the group had exposure exclusively to high levels for periods of 10 or more years. And only 66 of the 163 individuals had 10 years or more of exposure.

The importance of both duration and level of exposure on the development of a malignancy is reflected in the fact that seven of the nine malignancies which did occur in this group were in men with more than 10 years of exposure to high levels. It is possible that the malignancy rate might have been even higher if more of the men had exposure for 10 years or greater to 200 to 300 ppm (512,000 to 768,000 $\mu g/m^3$) of vinyl chloride.

6.3.2.3 *Harvard University Study*–Monson et al.[24,67] conducted a proportional mortality study among workers in a VC plant in Calvert City, Kentucky, and among workers in a vinyl chloride polymerization plant in Louisville, Kentucky. Death certificates were used as a source of cause of deaths, and were obtained for 142 out of 161 of the white males who were employed at these plants and were known to be dead. When death certificates were not available, cause of death as recorded in company abstracts was used. Causes of 161 deaths were tabulated for the period 1947-1973, and these were compared with the expected distribution of deaths as calculated from proportional mortality ratios for U.S. white males, taking into account age and time of death. Since mortality patterns among workers in both plants were similar, these groups were combined for purposes of data analysis.

Overall, a statistically significant 50 percent excess in deaths due to cancer was observed. Five cases of liver angiosarcoma were identified, in addition to one cancer of the gall bladder, one of the common bile duct, and one unspecified case of liver cancer. All told, a 900 percent excess was observed in cancers of the liver and bilary tract. Excluding angiosarcoma cases from this analysis, a 275 percent excess was observed in the remaining cancers. Five cases of brain tumors also were found, as were 13 cases of lung cancer, representing 320 and 60 percent excesses above the expected frequency of these cancers, respectively. A 100 percent excess in deaths due to suicides also was noted.

In addition to these overall cancer excesses, an increasing trend of cancer deaths with time was observed. No excess deaths due to cancer were observed prior to 1965. However, in the period 1965-1969, about a 50 percent excess in total cancers was observed, and in the period from 1970 on, a 100 percent excess. (This trend is generally consistent with the clustering in recent times of reported occupational cases of liver angiosarcoma.)

These data imply that at least two other forms of cancer, lung and brain, in addition to liver cancer, are increased among vinyl chloride workers. The experimental design did not permit the absolute risk of death in the study population. However, the observed excesses in specific cancers combined with the time trend for all cancers was considered by the authors to suggest a relationship between exposure to vinyl chloride in the work environment and cancer at multiple sites.

6.3.2.4 *Mount Sinai Study*–Nicholson et al.[68] utilized labor union and company records to identify a cohort of 257 individuals, each with a history of occupational exposure to VC in a polymerization plant for at least 5 years subsequent to 1946. This cohort included all individuals employed in this plant during the period 1946-1963. The mortality status of these individuals was evaluated from the 10th anniversary of their employment through April 1974. The minimum 5-year exposure criterion was established to focus upon the effects of significant durations of exposure. Beginning observations after only 10 years or more since onset of first exposure emphasizes the possible long-term effects of VC. The majority of individuals in this cohort, however, were exposed to VC for a period of 20 years or under.

This cohort represents a relatively young group since over half of the men were under age 37 when they entered the cohort. Over half of the men are presently employed in the PVC production facility, although not all in locations with VC exposure.

Of the 257 individuals in this cohort, 255 (or 99 percent) were successfully traced and their current health status evaluated. The majority of these men were directly employed in production although maintenance men and nonproduction workers were also included. Thus, exposures varied considerably among study subjects. No measurements of actual exposures were available. Over half of the workers in this cohort reported experiencing symptoms of dizziness, headache, or euphoria during work periods; 14 had experienced episodes of loss of consciousness. The authors concluded that peak VC exposures in this production facility may often have exceeded 1000 ppm (2560 mg/m^3) and may occasionally have approached 10,000 ppm (25,600 mg/m^3).

Included among the 24 deaths identified in this cohort were three confirmed cases of angiosarcoma of the liver. These preliminary findings suggest an excess of 25 percent in all deaths and a 131 percent excess in all cancer deaths although in neither case did these excesses reach statistical significance. In addition to liver angiosarcoma, one brain cancer and two lymphomas were observed, causing the authors of this study to suspect a possible relationship between VC exposure and these rare cancers.

6.3.2.5 *NIOSH Study*–A study of mortality and morbidity among current and past employees at two vinyl chloride polymerization facilities was conducted by the National Institute of Occupational Safety and Health (NIOSH).[58] The criteria for selection of facilities studied were, in order of decreasing priority: (1) involvement in the polymerization of vinyl chloride for at least 15 years, (2) existence of a sizeable work force, (3) location in a state where vital statistics are easy to obtain, and (4) existence of a medical program in the plant.

Since cancer often takes many years to become clinically evident, the study population was restricted to individuals with 5 or more years employment and at least 10 years since the beginning of employment in departments directly involved in polymerization of VC. The study population consisted of 930 white males. Attempts were made to trace study members from the time they terminated employment to December 31, 1973. The authors were unable to trace 285 individuals (31 percent); hence the mortality experience of these people compared to those who were traced is unknown. All individuals not traced were considered to be alive and were included in the analysis, thereby making any findings of increased mortality in this study cohort a conservative estimate of risk. Observed risks of death in the study population were compared to expected risks based upon mortality rates for the general white male population of the United States. Measurements, or estimates, of previous exposure levels to VC were not included in this study.

A total of 109 deaths were observed among these polymerization workers compared to 105 which would have been expected. This difference is not statistically significant; however, most occupational groups have a favorable mortality experience compared to the general population. Any deaths in the 31 percent not traced would have increased the observed number of deaths. An evaluation of specific causes of death indicate that, except for cancer, causes of death in the study group did not differ from those expected in the general population. However, a statistically significant ($p<0.01$) 57 percent excess in cancer deaths was observed above the expected. Excess cancer deaths were not limited to any single organ system -excesses being observed for cancers of the respiratory system, blood forming tissues, and the brain and central nervous system. Deaths due to liver cancer in this population were about 12 times above the expected number, and brain cancer deaths were fivefold higher. These latter contrasts were statistically significant ($p < 0.01$ and $p< 0.05$, respectively). The report does not state whether excesses in liver cancer other than angiosarcomas were observed. The majority (25 out of 31) of observed cancer deaths in this study population did not occur until at least 15 years following first exposure to VC.

6.3.2.6 *Comparison of Mortality Studies*–A comparison of the mortality studies shows reasonably consistent results; that is, an overall excess in cancer mortality among workers exposed to VC for long durations (Table 6.22). Both the NIOSH and Mt. Sinai studies, which employed the same study criteria, suggest increased overall mortality among these workers, but neither comparison shows statistically significant differences. In all five studies, workers exposed for 5 or more years to high levels of VC had greater than expected frequencies (ranging from 41 to 150 percent) for all cancers; however, in only two studies (NIOSH and Harvard) were these excesses statistically significant at the 0.05 level or lower.

In evaluating these observed mortality effects among VC workers, it must be recognized that the workplace situation may include exposures to other carcinogens and/or liver toxins in addition to VC and that any one of them may have contributed to the observed effects. While this situation makes it difficult to draw final conclusions from these human studies with regard to the role played by VC in the development of liver and other cancers, toxicologic studies have observed liver angiosarcoma and other cancers in mice, rats, and hamsters following inhalation exposures to VC at concentrations of 50 ppm (128,000 $\mu g/m^3$) and higher.[25,7,5] The liver angiosarcoma lesions observed in these animal studies, combined with the human observations in industry, strongly indicate that VC exposure is etiologically related to liver angiosarcoma in man.

With respect to levels of vinyl chloride exposure required to produce liver angiosarcoma, most, but not all, occupational cases reported to date have occurred among PVC workers and consequently may generally have involved TWA exposures in excess of 200 ppm (512,000 $\mu g/m^3$) with peak excursions in excess of 1000 ppm (2,560,000 $\mu g/m^3$). The most definitive evidence for past exposures among these workers comes from actual 8-hour average air measurements ranging from 120 to 385 ppm (307,200 to 985,600 $\mu g/m^3$) and excursions of 2000 to 4000 ppm (5120 to 10,240 mg/m^3) among highly exposed PVC workers at the Dow Chemical Company from 1950-1959.[69] Evidence of peak exposure excursions in excess of 1000 ppm (2,560,000 $\mu g/m^3$) among PVC workers in past years is also derived from the frequent reports of neurological symptoms among such workers. Existence of odors attributed to VC for much or part of the workday at these plants would tend to support these observations since the odor threshold for vinyl chloride is believed to be 250 ppm (640,000 $\mu g/m^3$) or higher.[69]

Reports of liver angiosarcoma among workers exposed to VC but not involved in the production of PVC, however, including that of an accountant in a U. S. vinyl cloth plant would tend to argue that at least for some individuals, liver angiosarcoma may occur at much lower exposures than encountered among PVC workers. Cases of liver angiosarcoma are reported in a worker employed at a VC monomer plant in Sweden and in a worker from England employed at a vinyl cloth plant.[58] Data from the Dow Chemical Company[69] show TWA exposures at monomer plants in the years 1973-1974 to generally be under 10 ppm (25,600 $\mu g/m^3$) although short-term exposures in excess of 100ppm(256,000 $\mu g/m^3$) have been reported. A survey by the National Institute of Occupational Safety and Health has shown VC levels in fabricating plants to

Table 6.22. COMPARISON OF MORTALITY STUDIES AMONG WORKERS EXPOSED TO VC

Factor	Tabershaw/Cooper study[64]	Dow study[65]	NIOSH study[58]	Mt. Sinai study[68]	Harvard study[67,68]
Number of plants	33	1	2	1	2
Study population					
Years exposed	1 or more	1 or more	5 or more	5 or more	No restriction
Onset since first exposure	No restriction	No restriction	At least 10 yr	At least 10 yr	No restriction
Size of cohort	8384	522	930	257	–
Number successfully followed up	7128 (85%)	505 (97%)	645 (69%)	255 (99%)	– –
Number of deaths	352	78	109	24	161
SMR's or relative risk					
All causes of death	75	91	103	126	–
All cancer deaths	110 (total) 114 (only those with 5 yr or more exposure)	84 (total) 250 (only those with high exposure with at least 15 yr after onset of exposure)	157[a]	231	150[b]
Multiple cancer sites suggested	Yes	Yes	Yes	Yes	Yes
Angiosarcoma of the liver found	Yes	No	Yes (?)	Yes	Yes

[a] Statistically significant at $p < 0.01$.
[b] Statistically significant at $p < 0.05$.

range from 1 to 12 ppm.[71] In the case of workers at fabricating plants, vinyl chloride exposures may result in part from release of trapped monomer in the PVC during processing and/or from inhalation of PVC dust containing entrapped monomer. While it is difficult to reconstruct exposures to vinyl chloride in these instances, it is likely that exposures for the workers involved in the fabrication process are considerably less than those for workers involved directly in the production of the monomer or the polymer.

6.3.2.7 *Infanté Study in Ohio*[33] –A study of the distribution of congenital anomalies was undertaken in residents living in three northeastern Ohio communities of Painesville, Ashtabula, and Avon Lake, where vinyl chloride production facilities are located. The population of the three communities ranges from 24,000 in Ashtabula to 12,000 in Avon Lake. The vinyl chloride production facility in Ashtabula began operations in 1954; the one in Avon Lake in 1946. Of the two plants located in Painesville, one began operation in 1946 and the other began in 1967.

The number and rates of children with congenital malformations in the three cities were computed and these observations were compared to an expected value derived from the congenital malformation rate in the entire state. The difference between the observed and expected numbers of malformations in each city was significant at $p < 0.01$ level (Chi Square). When all three cities were combined, the difference between observed and expected was significant at $p < 0.001$.

When birth malformations in the three cities were compared to congenital malformations for residents living in the remainder of the three counties in which the cities were located, the difference between the number of malformations per 1000 live births between the cities and the counties was significant at $p < 0.001$.

Malformation rates were computed for nine cities in the vicinity of the index communities and two of the nine had significantly greater numbers of malformations than expected. One community, Geneva was located 12 miles from Ashtabula and a second community, North Ridgeville, was located 8 miles from Avon Lake.

Significant excess of defects of the central nervous system, upper alimentary tract, genital organs, and club foot were observed in the study communities.

The observed differences could not be attributed to differences in race, maternal age, or reporting.

The number of deaths from central nervous system (CNS) tumors in the white population aged 45 years and older for the period 1958-1973 was significantly greater ($p < 0.01$) in the combined communities of Ashtabula, Avon Lake, Painesville, and North Ridgeville than in the one comparable group for the state as a whole. The excess number of CNS tumor deaths in white males in Painesville and North Ridgeville corresponds with an excess of CNS anomalies among stillbirths and live births in the two communities.

Limitations of the study:

- No consideration was given to other factors which can contribute to mutagenesis, teratogenesis, and carcinogenesis such as genetic factors, exposure to background radiation, other industrial exposures, and experience with infectious agents such as certain viruses.
- No information on exposure to vinyl chloride either in the occupational setting or in ambient air is presented in the paper. It is not known whether the plants have used the vinyl chloride monomer or polymer.
- It is not known whether the congenital anomalies occurred in families with occupational exposure to vinyl chloride or in families without occupational exposure which would then suggest ambient exposure.

Despite these limitations, the findings in this study suggest that exposures to vinyl chloride either from an occupational setting and/or ambient air may contribute to excess risk of anomalies particularly of the central nervous system. This area deserves further study.

A subsequent study by the Cancer and Birth Defects Division of the Center for Disease Control[72] confirmed a moderate increase in CNS malformations in Painesville, Ohio, but could not establish any association between cases and vinyl chloride exposure.

6.3.2.8 *SUVA Study (Organization of Insurance Carriers in Switzerland)*[73]–During the period from February to August 1974, the 62 persons involved in vinyl chloride fabrication and the 33 persons involved in vinyl polymerization in Switzerland were subjected to in-depth examinations. No evidence of illness was found among the workers. The average length of exposure was 13 years in the fabrication plant and 17 years in the polymerization plant.

No information was provided on exposure levels to vinyl chloride nor was there a description in the report of the type of clinical assessment carried out on the workers.

6.3.3 Nonmalignant Effects

In addition to the carcinogenic effects of VC, a considerable body of evidence has become available relating to nonmalignant effects, including reactions of the liver. The vast majority of evidence in this regard comes from observations among industrially exposed individuals.

Lester et al.,[74] in 1963, conducted animal and human acute toxicity experiments with VC. Three men and three women were exposed for 5-minute periods twice each day, separated by a 6-hour interval, for three successive days to VC concentrations up to 20,000 ppm (51,200 mg/m^3). Acute toxic effects (dizziness, nausea, dulling of visual and auditory cues, and headaches) were observed at concentrations above 8000 ppm (20,480 mg/m^3).

Kramer and Mutchler[53] correlated clinical and environmental measurements for 98 healthy male workers exposed to VC for periods up to 25 years. Exposure indices were based upon actual air measurements since 1950 and expressed as cumulative dosage (ppm-years) and career time-weighted averages, considering the time each worker spent in critical job classifications. History, physical examination, and laboratory tests were determined on exposed workers in other departments. Of 21 clinical parameters studied, six–systolic and diastolic blood pressure, BSP retention, icterus index, hemoglobin, and beta-protein–showed significant correlations ($p < 0.05$) with exposure variables, cumulative TWA, and cumulative dose. The best correlation (coefficient of multiple determination, 0.4) was between exposure and BSP retention, which is a measure of liver cell damage. Based upon these observations, the authors considered the possibility that "...repeated exposure to vinyl chloride at TWA levels of 300 ppm (768,000 μg/m^3) or above for a working lifetime together with a very low level of vinylidene chloride may result in slight changes in certain physiologic and clinical laboratory parameters. The possibility of some impairment in liver function must be considered even though no overt clinical disease was evident in any of the individuals studied."[53]

The BSP test is an insensitive index of overall liver cell function. Therefore, when the BSP test shows abnormal results, the liver is already extensively damaged. At present, it is a widely used and useful liver function test. BSP (Bromsulphalein) is taken up rapidly by liver cells, concentrated and stored within the cytoplasm, and conjugated enzymatically with glutathione. In diseases that produce hepatic cell dysfunction, significant quantities of unconjugated BSP may reenter the blood stream and be retained in the body.[74]

It is noteworthy that a good dose-response relationship between BSP retention and career TWA exposure was observed over the entire range of exposures examined. Based upon the derived regression equation, BSP retentions of 12.5 percent were expected among those with TWA's of 300 ppm (768,000 μg/m^3) and 5.6 percent among those with TWA's of 100 ppm (256,000 μg/m^3). A BSP retention in excess of 5 percent is considered to be abnormal in clinical medicine and suggests that substantial damage to liver cells may have occurred.[75] Judging from the data as presented, a small fraction of individuals with career TWA's of 50 ppm (128,000 $\mu g/m^3$) had abnormal BSP retention tests suggesting that liver damage had occurred. Exposure to other liver toxins such as alcohol was not adequately considered in this study.

Observations of liver damage among workers who fabricate PVC plastic into finished products as well as among workers who convert VC monomers into the polymer indicate that injury to the liver among exposed workers is important and that such damage may occur at lower levels of exposure than is usually encountered in the production of PVC.

These data suggest that exposure to 50 ppm VC (128,000 $\mu g/m^3$) is associated with increased BSP retention and the evidence is greater in VC/PVC workers than in the general population.

In German studies, enlarged livers and spleens, as well as abnormal results of tests of liver function, were found in PVC production workers.[76,77] Microscopic examinations of biopsy specimens revealed evidence of liver pathology in a high percentage of cases. These workers had a history of employment ranging from 1.5 to 21 years. No measures of past VC exposure were available, and it is not known whether adequate comparisons were made with control groups (see Table 6.23). Further, Table 6.23 shows increased BSP retention in workers involved in processing the polymer, which is consistent with the findings of Kramer and Mutchler.[53]

Following these initial reports of liver damage in PVC production workers from Germany, additional studies were carried out in 50 individuals with varying durations of exposure to VC during the production of PVC.[78] These studies indicated that there was a relation between the duration of exposure to VC and the severity of liver damage, as determined by microscopic examination of biopsy specimens. The most severe evidence of liver pathology was among 16 workers with exposure in excess of 10 years. All exhibited evidence of liver abnormality, and two cases of liver angiosarcoma were observed. All of the German workers, with exposure lasting 3 years or less, had some form of liver damage, although generally not as severe as that found in workers with longer exposures. Five workers who were involved in postpolymerization of VC were examined, and all five showed signs of minimal damage to the liver parenchymal cells.

Although these studies do indicate a relationship between exposure duration and histologic evidence of liver damage, the lack of exposure data on these workers makes it difficult to determine what levels of exposure may have been responsible for such damage. Failure to compare exposed workers with a suitable control group not exposed to vinyl chloride and failure to consider the effect of alcohol intake are other limitations which deserve mention.

Examinations of 70 out of 128 workers in a PVC production plant revealed evidence of extensive abnormalities based on biochemical indicators and other tests.[79] These workers were employed an average of 7.7 years in the industry (range 6 months to 21-3/4 years). Upper abdominal complaints were present in 42 of 70 workers, and symptoms such as tiredness, dizziness, parasthesias, and arthralgia were frequently reported. Thrombocytopenia, increased BSP retention, and splenomegaly were present in a majority of cases, 81, 67, and 57 percent, respectively. Reticulocytosis was also common (41 percent), and abnormal liver enzymes, esophageal varices, and leucopenia were also observed. Unfortunately, effects of exposure, both level and duration, were not evaluated in this study. Further, the frequency of abnormal findings among workers not exposed to vinyl chloride was not studied so that it is difficult to accurately judge the effects of such exposure. Findings such as splenomegaly, thrombocytopenia, and increased BSP retention in the majority of instances does, however, suggest that damage in excess of the expected frequency among the general population had occurred in these workers, though these changes were not necessarily specific for vinyl chloride.

Additional studies were carried out among workers in Germany employed in PVC processing plants.[80] Such workers would have had a somewhat lower exposure than those involved in the direct polymerization of PVC from the monomer. Medical examinations were conducted on 15 such workers who were employed an average of 5 years, ranging from 1.5 to 13 years. Seven complained of pressure and/or pain in the upper abdomen. Thrombocytopenia and increased BSP retention were found in 7 of 25 workers, although not necessarily concommitantly. One worker had an enlarged spleen. In biopsy specimens from four workers, one showed histologic evidence of liver damage similar to, although less severe than, that observed in PVC production workers.

Creech and Makk[81] studied liver disease among PVC workers at the B. F. Goodrich plant in Louisville, Kentucky. A total of 1183 employees had blood tests to screen for evidence of liver damage. These workers included individuals not involved in the direct production of PVC, such as maintenance personnel, administrators, and secretaries. On initial screening tests, 315 of 1183 (26.6 percent) showed at least one abnormal blood test, and 41 (3.5 percent) had two or more abnormal tests. Among the 315 tested for a second time, 75 had a persistent abnormality. The most common observed abnormality in this test was an elevated alkaline phosphatase, although increased bilirubins and serum glutamic-oxaloacetic transaminase (SGOT's) also were observed. Based upon this initial battery of screening tests, 116 individuals were given more extensive blood tests; some abnormalities were found in 59 (about 50 percent) of those examined. Seven of these individuals had major abnormalities that required additional test procedures. The highest percentage of abnormal batteries of tests (10.9 percent) occurred among PVC production workers; although abnormal batteries also were found in other production workers, in maintenance workers, and in clerical personnel.

Depending upon results from the battery of tests, more elaborate diagnostic procedures such as liver scans, hepatic arteriograms, and liver biopsies were initiated. Of 17 individuals undergoing such tests, 11 cases of portal fibrosis, indicating severe damage to the liver, were discovered. Two cases occurred among workers not directly involved in the production of PVC. Angiosarcoma of the liver was found in 2 of the 11 workers–both were involved in PVC production.

While this study in Louisville did document evidence of damage related to vinyl chloride, i.e., liver angiosarcoma, the extent to which less severe liver damage may or may not be related to vinyl chloride is not at all clear from this study. Although there is suggestive evidence that less severe damage may also have occurred, adequate comparisons were not made with matched control groups, and measurements of vinyl chloride exposure were not made. Accordingly, level of exposure could not be related to observed effects. Failure to correlate abnormal tests with duration of exposure or with latent period since onset of exposure, and lack of consideration of alcohol intake are additional limitations in this study.

Miller et al.[82] examined the work force at a PVC production plant in Niagara Falls. Duration of exposure and alcohol intake were considered, but exposure was not measured directly. A total of 354 workers was examined, 267 currently employed in a vinyl chloride polymerization plant (encompassing the entire work force), and 87 former workers. Hepatosplenomegaly was observed in a high percentage of current and former workers (15.0 and 3.4 percent, respectively), with the most frequent occurrence in each category among workers exposed for 20 or more years. Hepatosplenomegaly was observed among 6 percent of the current workers with not more than 2 years' exposure, but was less frequent among former workers. Nearly one-third of the current workers exposed for 20 or more years showed enlarged livers or spleens. Hepatosplenomegaly generally was higher in each exposure category among those with a history of significant alcohol intake compared to those with no significant intake. In each group, the frequency of hepatosplenomegaly was related to duration of work exposure. Tests of liver enzymes were also abnormal, even among those with exposure of not more than 2 years' duration, and these abnormalities were generally more frequent with longer exposures. Elevated alkaline phosphatase, the most frequently observed biochemical abnormality, did not correlate well with ethanol intake, but did correlate significantly with duration of exposure to vinyl chloride.

In addition to finding evidence of liver dysfunction in these workers, the study showed that abnormal pulmonary function and chest X-rays also were associated with longer exposures to VC.[83]

While the association of abnormal findings with duration of exposure to VC suggests an effect relationship, these results were not compared with the frequency of abnormalities in a matched control group.

Table 6.23. SYNOPSIS OF ANAMNESTIC, CLINICAL, BIOCHEMICAL, PERITONEOSCOPIC AND HISTOLOGIC DATA OF 50 PVC WORKERS[11,a]

No.	Nationality	Age, yr	Job classification	Exposure, yr/mo	Alcohol intake, g/day	Central nervous symptoms	Upper abdominal discomfort	Hepatomegaly[b]	Splenomegaly[b]	Serum bilirubin (>1.0 mg/100 ml)	BSP retention (>5% after 45 min)	SGOT (>12 (18) mU/ml)	SCPT (>12(22) mU/ml)	Alkaline phosphatase
1	Ger	50	PM	21/9	–	+	+	1.5			8.7	15	15(23)	
2	Ger	56	PM	18/6	16–32	+	+	2	2		6.1			
3	Ger	47	PM	18	–	+		3	5		15.6	13	19(24)	92
4	Ger	46	PM	17/6	8	+	+			1.1	10.2	13(22)	15(47)	
5	Ger	51	PM	17	48-64			3	1.5		9.1	19	17	
6	Ger	51	PM	16	16		+	1			11.3			
7	Ger	52	PM	15/3	8	+	+	2	(2)	1.2	16.7	25	22	83
8	Ger	53	PM	14/6	8	+	+	1.5			5.6	15		
9	Ger	44	PM	13/9	8			1.5				15	13	
10	Ger	39	PM	13/9	16		+	3	(11)	2.0	17.6	31	23	85
11	Ger	48	PM	13	16–32		+		1.5		6.2	15	15	
12	Ger	27	PM	12/6	–	+						13		
13	Gr	40	PM	12/3	28		+			1.1			13	
			PC	0/9										
14	Ger	52	PM	11	–	+	+	2	11	1.1	13.0	16	16	
15	Ger	35	PM	9	16				3	1.1	15.1	19	17(31)	50
16	Gr	45	PM	8/6	16						8.8	13	13	
17	Gr	42	PM	6/8	8	+	+	2			13.8	25(24)	23(63)	
			PC	4/0										
18	Ger	54	PM	6/6	16	+	+	10	(10)	1.4	6.9	(20)	(27)	58
19	Ger	31	PM	5/9	16		+						(28)	
20	Turk	33	PM	5/9	8		+					15		
21	Gr	30	PM	5	8		+				9.6	15	13	
22	Ger	34	PM	5	16	+	+		1.5		21.5	21(21)	23(40)	
23	Gr	36	PM	5	16		+				7.6		25	
24	Gr	30	PM	5	8	+	+	1.5	6	1.8		90	190	
25	Gr	35	PM	4/9	16	+	+	1.5			8.5	32(27)	30(40)	
26	Ger	30	PM	4/9	16–32		+	3			7.5	15	15(24)	
27	Ger	31	PM	4/9	8	+	+	1.5			8.3	15	15	
28	Gr	31	PM	4/0	–	+	+		6	1.7	7.1	23	25	
			PC	1/0										
29	Turk	33	PM	4/0	8	+	+	6	3	1.8	25.6	25	58	66
30	Gr	30	PM	3/9	4	+	+	1.5			6.4	15	17	
31	Turk	36	PM	3/9	?	+	+	1.5	1.5	2.2	22.5	25	34	68
32	Turk	33	PM	3/6	–			3			6.8	23	17	

			Peritoneoscopy			Histology						
Acroosteolysis	Raynaud like phenomenon	Skin lesions	Surface relief	Capsular fibrosis	Capsular vessels	Collagenization of sinusoidal walls	Enlargement and/or proliferation of littoral cells	Septal fibrosis	Spleen size by scintigraphy, cm	Enlargement of spleen	Esophageal varices	Thrombocytopenia ($>150 \times 10^3/\text{mm}^3$)
				R		(+)	+		Normal (liver scan)			+
				R	A/I	+	+	+	15 x 11 x 12	+		+
	(+)		G/Nod	R	?	+	++	+	Markedly enlarged (liver scan)	+	+	+
			U/G	R/S	A	+	+		12 x 7 x 11	+		
			Nod	R/S	A	+	+		14 x 12 x 6	+	+	+
	+		G	R/S		+	+	(+)	12 x 9 x 9	+		
	(+)		U	?	?	+	(+)	+	Splenectomy (15 x 12 x 7)	+	+	+
			G	R/S		(+)	++	+	10 x 8 x 4			+
			U	R		+	(+)	+	10 x 8 x 5			+
			G	R/S	I	(+)	+		24 x 12 x 7	+	+	+
			G/Nod	R/S	I	+	+		15 x 11 x 7	+		+
			G	R/S	A	+	(+)	(+)	14 x 5 x 12	+		+
				R		(+)	(+)		Normal (liver scan)			+
			G	R	I	+	+++	+	23 x 14 x 9	+	+	+
		+	G		A	Not examined			13 x 10 x 5	+	+	+
				S		+	(+)	(+)	12 x 9 x 5	+		+
			U	R	A	+	(+)		Normal (liver scan)			
			G	?	?	+	(+)	++	Splenectomy (500 g)	+	+	+
			G	S	A		(+)	(+)	23 x 10 x 18	+	+	+
			G	C/R		+	(+)		18 x 11 x 12	+		+
						+	(+)		14 x 12 x 13	+		+
+		+	Not examined			(+)	+		15 x 9 x 10	+		+
				R		+	+		14 x 9 x 10	+		+
				R		+	(+)		17 x 12 x 14	+	+	+
				R		+	(+)	+	13 x 10 x 10	+		+
			U		A	+	+	(+)	14 x 6 x 8	+		+
				R		+	+		13 x 9 x 14	+		+
			U	S/PC	A		(+)		16 x 10 x 4	+		+
+	(+)	+	G	R					14 x 13 x 6	+		+
				R	A	(+)	+	(+)	Normal (liver scan)			+
+	+	+	G	?	A	+	+		14 x 6 x 11	+		+
+	(+)	+		R	A	+	(+)		13 x 5 x 11	+		+

Table 6.23 (continued). SYNOPSIS OF ANAMNESTIC, CLINICAL, BIOCHEMICAL, PERITONEOSCOPIC AND HISTOLOGIC DATA OF 50 PVC WORKERS[11,a]

No.	Nationality	Age, yr	Job classification	Exposure, yr/mo	Alcohol intake, g/day	Central nervous symptoms	Upper abdominal discomfort	Hepatomegaly[b]	Splenomegaly[b]	Serum bilirubin (>1.0 mg/100 ml)	BSP retention (>5% after 45 min)	SGOT (>12 (18) mU/ml)	SGPT (>12(22) mU/ml)	Alkaline phosphatase
33	Ger	32	PM PC	3/6 1/0	4	+	+	6	4		12.5	19	16	
34	Ger	40	PM	3/6	16		+	1.5		1.1	8.6	19(20)	15(31)	
35	Gr	31	PM	3/3	8–16		+				5.2	(20)		
36	Gr	38	PM	3/3	8–16 (110– 160)							13	15(24)	
37	Gr	47	PM	3/0	16	+	+	3			9.7			
38	Gr	30	PM	3/0	–	+	+	3				13		
39	Turk	30	PM	2/9	–			1.5			8.4	17	13	
40	Gr	33	PM	2/6	–			1	1					
41	Gr	41	PM	2/3	16	+	+	1						
42	Ger	41	PM	1/9	8		+				6.1	19(22)	17(47)	
43	Gr	36	PM	1/6	8			3			6.3	17	17	56
44	Turk	33	PM PC	0/9 0/3	8						5.1	28	30(23)	66
45	Gr	48	PC	13/0	14		+	7			9.1	13(33)	13(80)	
46	Gr	44	PC	9/0	28						15.1	15	17	
47	Gr	39	PC	5/3	16		+					(20)		58
48	Gr	45	PC	4/6	–		+				8.8	(22)	(47)	
49	Gr	37	PC	4/0	44	+		6			7.0	(88)	(72)	110
50	Ger	36	PC	2/0	32	+	+	8				28(20)	28(38)	

[a] Abbreviations used are: *Nationality:* Ger, German; Gr, Greek; Turk, Turkish; *Job Classification:* PM, VC polymerization; PC, processing of the polymer; *Peritoneoscopy:* U, slightly irregular or undulated; G, granular to finely nodular; Nod,

[b] Centimeters below costal margin.

Acroosteolysis	Raynaud like phenomenon	Skin lesions	Peritoneoscopy			Histology			Spleen size by scintigraphy, cm	Enlargement of spleen	Esophageal varices	Thrombocytopenia ($>150 \times 10^3/\text{mm}^3$)
			Surface relief	Capsular fibrosis	Capsular vessels	Collagenization of sinusoidal walls	Enlargement and/or proliferation of littoral cells	Septal fibrosis				
+	(+)	+	U/G	S		+	+		14 x 9 x 7	+	+	+
	+	+		R	I	+	+		Slightly enlarged (liver scan)	+		+
				C	A	+	(+)		13 x 7 x 9	+		+
			U	C		+	(+)		10 x 9 x 7	+		+
				(S)	A		(+)		12 x 6 x 8	+		+
				C/R		+	+		15 x 12 x ?	+		+
							+		16 x 6 x 8	+		+
			U	C/S	A	+	(+)		13 x 7 x 12	+		+
			G/Nod	C/R/PC	A		(+)		11 x 7 x 10.5	+		+
			G/Nod	S		+	+	+	12 x 9 x 7	+		
				R			(+)		11 x 8 x 5			+
							+		12 x 8 x 6	+		+
							(+)		Normal (liver scan)			
				(R)			(+)		9 x 6 x 6			+
				(R)		(+)	(+)		12 x 8 x 9	+		
				R/PC	A	+	(+)		Normal (liver scan)			+
				S	A	+	+		11 x 5 x 7			
				C	A	+	(+)		12 x 6 x 11	+		

coarsely nodular; C, comma-like or stellate; R, finely to coarsely reticular; S, small scar-like patches to broader concave postnecrotic scars; PC, patchy "perihepatitis cartilaginea;" A, augmented; B, increased; *Histology:* (+), minimal; +, slight; ++, moderate; +++, marked.

Not all U.S. studies observed effects among workers exposed to VC. One negative study involved an evaluation of health surveillance data on 335 workers exposed to VC at Dow Chemical Company.[84] This survey was based upon a multiphase screening program. The study population was comprised of production employees who had worked for at least 1 year between 1942 and January 1972 in areas with potential VC exposure and who were also employees at the Dow Midland Division between February 1967 and March 1974, the period of the multiphasic health screening program.

Exposure categories were based upon industrial hygiene data compiled from 1950 on, using estimated time-weighted average concentrations for an 8-hour day. The high exposure group was defined as those with exposures above 200 ppm (512,000 $\mu g/m^3$) for a duration of 1 month or longer; the intermediate group had exposures from 25 to 200 ppm (64,000 to 512,000 $\mu g/m^3$); and the low group had exposures under 25 ppm (64,000 $\mu g/m^3$). A fourth exposure category, undefined, was established for those individuals without sufficient industrial hygiene data. A subjective evaluation indicated that most individuals in this latter group were exposed in the low to intermediate range. The participation rate in the multiphasic screening program was about 80 percent in all exposure groups. Measured exposure data were available for most of the workers. By definition, the high exposure group may have included individuals with predominantly low-level exposures throughout the majority of their work experience, but the lowest exposure category would not have included workers with a history of high-level exposure to vinyl chloride.

Because of revisions in the multiphasic screening program in 1970, the data obtained before and after this date were analyzed separately. A control group of matched pairs for sex, age, smoking history, and month of examination, and, where possible, date of hire was included in the analysis. The parameters studied prior to 1970 included tests of pulmonary function, blood pressure, white blood count, total bilirubin, serum glutamic-pyruvic acid transaminase (SGPT), and alkaline phosphatase. The only statistically significant difference ($p < 0.05$) between exposed and matched-pair control groups was for decreased diastolic blood pressure in the high-exposure group. No differences between exposed and control groups were noted in terms of pertinent historical questions including shortness of breath, chronic cough, jaundice, gastrointestinal trouble, numbness in hands or feet, cancer, anemia, or blood problems.

The health surveys after 1970 included similar historical information and laboratory tests for pulmonary function, hemoglobin, white blood count, serum glutamic-oxaloacetic transaminase (SGOT), lactic acid dehydrogenase (LDH), total protein, protein albumin, and protein globulin. Statistical analysis of alkaline phosphatase was not performed due to changes in laboratory procedures. No statistically significant differences between exposed and control groups were found. The availability of measured exposure data and the comparability of laboratory results with the inclusion of matched-pair controls for each exposure category in this investigation are important factors not found in some other studies. Information was not available as to possible toxic chemical exposure in the matched-pair controls, and the impact of duration of exposure was not considered. Based upon the available data, the authors concluded "... below 200 ppm (512,000 $\mu g/m^3$) nothing of statistical significance has been observed."[84] It is unlikely that the high-exposure group was really exposed to TWA of 200 ppm (512,000 $\mu g/m^3$) over their full employment period, since high exposures of only 1 month's duration were sufficient to place an individual in this category. An earlier study at Dow Chemical Company suggested that liver damage may have occurred among some workers with TWA exposures of 50 ppm (128,000 $\mu g/m^3$).[53]

Kotin[85] reported the results of a study of currently employed workers exposed to VC at Air Products and Chemicals facilities in Calvert City, Kentucky, and at Pace, Florida. Also included were results of a death certificate survey of PVC employees who had left the company, or had died while employed at the company. A detailed medical history and physical examination (with X-rays and laboratory tests) were performed for each employee.

At Pace, 13 of 201 employees examined showed abnormal findings. Persistent minor abnormalities were found on retesting of three employees. These findings did not justify further immediate retesting, although retesting was scheduled 90 days later. The remaining six employees were given liver scans, all of which were normal. One case of acroosteolysis was found at Pace.

At Calvert City, 97 of 291 employees examined showed an abnormality on initial testing, partly due to equipment malfunction. Following retest, 29 employees showed persistent abnormalities; 16 were considered equivocal, not justifying further immediate additional testing, but indicating retesting 90 days later. Among the 13 employees who were immediately retested, six were found to need further laboratory and physical examinations. Of these, two cases of Gilbert's disease and two cases of gallbladder disease were found, including one with coexistent hepatitis. An additional case of chronic persistent hepatitis without gall bladder disease was found. Examinations of the death certificates did not indicate any relationship between exposure to vinyl chloride and cause of death. In light of these results, except for the one case of acroosteolysis, the authors concluded that there was not evidence to identify VC as a causative agent in disease. No cases of angiosarcoma were identified in this survey. Neither information on age, level and duration of exposure, or a definition of an abnormal test was given. Measurements of vinyl chloride exposure were not made, nor is there any indication as to what percentage of workers examined was suspected to have high vinyl chloride exposures. Workers who had left the plants were not included in the death certificate survey. The frequency of abnormal findings on physical examinations, particularly enlarged livers and spleens, was not indicated. Accordingly, an adequate latent period following onset of first exposure may not have been present to allow effects such as liver angiosarcoma to be evident.

Dernehl[70] surveyed 36 PVC plants to determine if there were factories in which no cases of liver angiosarcoma were observed. Plants in which angiosarcoma had occurred were not included in the analysis. Similarly, plants with operating experiences of 10 years or less were not considered. The remaining 16 plants included 2372 persons currently employed and 1471 previously employed. Included were 787 persons who had worked more than 10 years, and 104 who had worked more than 20 years with VC. Also included were 1402 persons with a time since initial exposure to VC of more than 10 years, and 416 persons with 20 years or more. Of these 16 plants, only 2 had conducted measurements of vinyl chloride concentrations prior to 1970. The presence of vinyl chloride odors was used to estimate past exposures in the other plants. The odor threshold for vinyl chloride is above 250 ppm (640,000 $\mu g/m^3$) and perhaps as high was 2000 ppm (5120 mg/m^3) for unacclimated workers. On this basis, 4 companies indicated that vinyl chloride odors were detectable for most of the work day prior to 1960; only 2 of 16 reported odors most of the day between 1960 and 1970; and no plants reported odors this frequently after 1970. All 16 plants reported the occasional presence of VC odors at some time in the past. Since January 1, 1974, 3285 examinations were conducted on employees in these companies, including 872 retirees. This constitutes a followup rate of nearly 90 percent of all employees, but only 60 percent of those who were previously employed. Of these, 3249 were given liver profile tests as included in the SMA-12, that is,bilirubin, SGOT, LDH, and alkaline phosphatase. An abnormality in one of these four tests was reported in 15 percent of those examined, but this fell within the limits of abnormality observed among 900 Union Carbide employees not exposed to VC and 400 office personnel with no known occupational exposure to the chemical. Similarly, the occurrence of abnormalities in two tests (2.7 percent) and in three tests (1.3 percent) were comparable to those found in control groups. No definition of an abnormal test was given. Based upon these observations, the author concluded that "Examinations of these men have failed to show the existence of abnormal liver function tests in greater proportion than would be found in a control population. There is no case of angiosarcoma of the liver among these 1402 men even though their exposure time is sufficient for disease to have occurred..."[70] It should be noted that less than 10 percent of these workers had direct exposure of more than 20 years'duration and 416 workers had a time lapse since first exposure of 20 years or more.

Considering the lack of information on control and exposed groups and the many laboratories participating in these analyses, it is difficult to draw any conclusions with regard to the frequency of abnormal liver function tests among these vinyl chloride workers. The fact that only 60 percent of former workers who have had the greatest durations of exposure were included in these examinations of liver function tests is a serious shortcoming, as is failure to examine the influence of duration of VC exposure upon abnormal liver function.

A summary of the data showing nonmalignant effects of vinyl chloride is shown in Table 6.24. The results of these studies and their limitations have been discussed above.

Table 6.24. SUMMARY OF OCCUPATIONAL FINDINGS RELATING NONMALIGNANT LIVER DAMAGE TO VINYL CHLORIDE EXPOSURE

Study group (number studied)	Level of exposure	Duration of exposure	Observed effects
PVC production workers[76,77]	Unspecified	1½ to 21 years	Enlarged livers and spleens. Abnormal BSP retention. Biopsy of liver showed portal fibrosis.
PVC production workers[64] – liver biopsy study[78]	Unspecified	3 years and under	Biopsy showed mild liver damage in all workers.
		10 years and more	Relation between duration of exposure and severity of damage with most severe liver pathology observed in workers with 10 or more years of exposure.
PVC polymerization workers[63] – liver biopsy study[80]	Unspecified	Unspecified	5 of 8 workers examined showed evidence of mild damage to liver parenchyma based on liver biopsy.
PVC production workers[79,95]	Unspecified	6 months to 21¾ years (average 7.7 years)	Upper abdominal complaints, lethargy, and paresthesias common complaints. Thrombocytopenia, increased BSP retention, and splenomegaly found in majority of workers.
PVC processing workers[81,84]	Unspecified	1½ to 13 years	7 of 15 workers complained of pressure or pain in upper abdomen and had thrombocytopenia and increased BSP retention. Biopsy showed mild liver damage similar to that in PVC production workers.
PVC production workers and non-PVC production workers (1183 total)[81]	Unspecified	Unspecified	116 of 1183 (about 10 percent) showed significant biochemical abnormalities. Abnormal liver function tests found in non-PVC production workers. 11 cases of portal fibrosis found on liver biopsy, 2 of which were in workers not directly involved in PVC production.
Current and former PVC production workers (354 total)[82,83]	Unspecified	$\leq$2 years	Hepatosplenomegaly observed in 6% of workers exposed not more than 2 years.
		5-10 years	Sharp increase in hepatosplenomegaly.
		20 years or more	Nearly one-third of workers had hepatosplenomegaly. Elevated alkaline phosphatase correlated with duration of exposure. Abnormal lung function tests found.

Table 6.24 (continued). SUMMARY OF OCCUPATIONAL FINDINGS RELATING NONMALIGNANT LIVER DAMAGE TO VINYL CHLORIDE EXPOSURE

Study group (number studied)	Level of exposure	Duration of exposure	Observed effects
PVC production workers[53]	TWA exposures up to 300 ppm	Up to 25 years	Abnormal liver function (BSP retention) correlated with TWA exposures. Evidence of abnormal BSP retention at TWA exposures of 300 ppm and suggestive evidence of BSP retention in some workers exposed to TWA of 50 ppm.
PVC and non-PVC production[84] workers (335)	TWA exposures of 25-200+ ppm	1 year and greater	No adverse effects related to angiosarcoma by any of the criteria studied below 200 ppm.
PVC workers (492)[58]	Unspecified	Unspecified	One case of acroosteolysis only evidence of injury attributable to VC.
PVC workers (3843)[70]	Estimated as greater than 250 ppm prior to 1960	Includes exposed 20 years and more	No increased abnormalities above levels in control groups.
PVC production workers (594)[65]	TWA exposures (8 hr day) < 25 ppm 25-200 ppm 200-300+ ppm	< 1 year > 1 year	No deaths due to angiosarcoma or other liver cancer. For workers exposed to >200 ppm, apparent increase in overall malignancy, not statistically significant.

These observations of liver injury among PVC workers, and particularly among workers not directly involved in PVC production, have potentially important implications with respect to the health of the general population exposed to vinyl chloride. In reviewing these findings it is, however, important to recognize that other toxic agents, either work or nonwork related, such as liver toxic drugs or alcohol, could have contributed to many of these abnormal findings. Further, some of the biochemical screening tests are not specific for liver injury, though others, such as BSP, are. Ideally, one would like to know the prevalence of liver injury among comparable nonindustrially exposed populations before drawing final conclusions regarding the effect of exposure to vinyl chloride upon the liver from the above studies. Most studies were lacking in this regard. In spite of difficulties with the present studies such as noted above, there is suggestive evidence presented for at least minimal liver damage associated with vinyl chloride, which may be observed with durations of exposure under 2 years. Though there is reason to believe that cessation of exposure to vinyl chloride would cause a reversal in some of this damage, there is also evidence that in some people, this damage is not fully reversible and may even progress further. For example, one vinyl chloride production worker examined by liver biopsy at the National Institute of Health showed persistent and perhaps progressive liver pathology 2-1/2 years after the cessation of exposure despite an absence of abnormalities in biochemical tests of hepatocellular function. There is also concern that the histologic changes in the liver observed in PVC workers may represent premalignant changes that would increase the risk of developing angiosarcoma in future years.

Any final conclusions regarding the implications of these findings for the general population who are exposed to levels of vinyl chloride in the air generally much lower than in occupational situations must await completion of additional studies. However, several observations do suggest that exposure to vinyl chloride in the air may pose some risk to health at these lower levels.

6.3.4 Ongoing Research in Health Effects from Vinyl Chloride

An attempt has been made to determine what studies are presently being conducted on VC. The following is a listing, obtained through personal communication,[86,87] of research that is presently underway, as well as preliminary findings as of June 1, 1975. This probably does not represent a complete listing and there may well be other studies of which the authors of the report were not aware.

6.3.4.1 *Studies by the Center for Disease Control*[87]–Drs. Henry Falk and John Herbert of the Cancer and Birth Defects Research Division are reviewing 300 reported cases of hepatic angiosarcoma and correlating as much background information on the victims as is available to determine possible causative agents. Drs. Hans Popper and Lou Thomas will review the pathological reports and specimens for verification of diagnosis.

Dr. William Flynn and Mr. Lawrence Edmonds are doing a follow-up of the Infanté study on birth defects in two communities in Ohio. Their study will attempt to determine if the nearby VC plants have any impact on the observed unusually high occurrences of central nervous system birth defects.

6.3.4.2 *Studies Funded by the Manufacturing Chemists Association*[87]–A 24-month study, using Dr. Maltoni's protocol, but restricted to 50 ppm and higher doses, has been in progress for over 18 months. The 12- and 18-month data have been correlated, and can be provided. Dr. J. C. Calandra of Industrial Bio-Tech Laboratories is conducting the study.

Drs. B. A. Schwetz and P. J. Gehring of Dow Chemical Company are directing a metabolism study. It has been completed, and results have been promised.

6.3.4.3 *Harvard University-Peter Bent Brigham Hospital Study*[87]–A study on endoplasmic acute liver injury by vinyl chloride has indicated that a single 6-hour inhalation exposure to vinyl chloride monomer (5 percent) produces extensive vacuolization of centrolobular liver parenchyma and focal midzonal necrosis in the hepatic lobuole in rats pretreated with 0.1 percent sodium phenobarbital in drinking water. Ultrastructurally, vacuolization consists of dilation of cysternae of rough endoplasmic reticulum and, in the same cells, smooth endoplasmic reticulum coalesces into discrete aggregates resembling denatured membranes. The findings support the hypothesis that vinyl chloride is hepatotoxic because it is converted into a toxic metabolite by components of the mixed-function oxidase system (MFOS) of liver endoplasmic reticulum.

In another study, preliminary findings indicate that single 6-hour inhalation exposures to vinyl chloride monomer (5 percent) produce acute liver injury in rats pretreated with sodium phenobarbital (400 μ mole/kg, daily, for 7 days, by gavage). Pretreatment with Arochlor 1254 in the same manner appeared to render animals exquisitively sensitive to VC, as shown by an increase in serum glutamic-oxalacetic transaminase (SGOT) of approximately 5 (for phenobarbitol) to 10 (for VC) times normal, respectively. If the activation of VC to a hepatotoxin occurs during metabolism, an initial reaction would most likely occur via the multimolecular MFOS, the enzyme system responsible for conversion of most xenobiotics to more readily excretable metabolites. This metabolism mechanism may lead to toxification or detoxification reactions. Correlations between induction of specific MFOS components and the degree of VC-induced hepatic traumas as measured by increased serum transamenase (SGOT, SGPT) at 24 hours following VC exposure reveal significant relationships between injury and increased NADPH cytochrome P-450 reductase activity (as measured by reduction of cytochrome C) and total cytochrome P-450 content. Injury appears related to morphologic changes in the endoplasmic reticulum. Hepatic injury following inhalation exposure to 1,1-dichloroethylene (0.02 percent) differs strikingly from that observed after administration of vinyl chloride, in that it appears to involve plasma membranes, mitochondira, and chromatin, but not the endoplasmic reticulum. In contrast to vinyl-chloride-induced reactions, induction of cytochrome P-450 appears to protect against 1,1-dichloroethylene.

6.3.4.4 *International Agency for Research on Cancer, Report of the Working Group*[88] –The IARC has held several meetings in an attempt to coordinate the various epidemiological studies being conducted in different countries on the oncological hazards associated with VC exposure. A primary consideration is the general terms of the types of studies needed to be done and the principles underlying their design. IARC recognizes the fact that cohorts need to be established now for long-term prospective followup; also, the failure of risk to become apparent after 10 years does not preclude the emergence of such a risk, perhaps at a different target organ, many years later. A figure of 90 percent was tentatively proposed as the minimum acceptable loss during followup of cohort. Attempting to unify the results of so many different studies, the IARC is considering the establishment of a pathology review panel, with the World Health Organization Cancer Unit, and a register of liver angiosarcomas, which would operate in conjunction with the registers of both the United States and the United Kingdom.

6.4 ECOLOGICAL EFFECTS

The possible ecological problems associated with release of vinyl chloride into the environment are just coming under scrutiny. For some time it has been known that the plastic polyvinyl chloride is not readily biodegradable. Microorganisms are not able to utilize the plastic or are able to do so only after an extended period of weathering. Although acetylene and ethylene are both capable of being reduced by microbial activity,[89,90] their chlorination seems to make them less amenable to attack by microorganisms. Available evidence does indicate that alkynes may be oxidized by peptone-grown pseudomonas species.[91] Very little is known regarding the biological metabolism of alkynes.[92] The fact that PVC is not readily biodegradable has led to the difficulties in disposal. Incineration, the chief means of disposal, is not without its problems. Though hydrogen chloride is evolved when burning refuse, the amounts released do not compare to those released when polyvinyl chloride and polyvinylidene chloride plastics are incinerated. Addition of polyethylene and polystyrene plastics to normal base refuse containing no plastics had no effect on chloride ion emissions because these plastics contain no chlorine. Addition of 2 percent polyurethane foam resulted in slightly increased chloride emission up to 689 ppm (1763 mg/m^3); with a 4 percent addition, emission increased to 751 ppm (1922 mg/m^3). Adding PVC to the normal refuse increased chloride ion emission to 1990 ppm or 5094 mg/m^3 (0.1990 percent) for the 2 percent addition, and to 3030 ppm (7756 mg/m^3) for the 4 percent addition.[93] During burning, most of the chloride present in refuse and in the polyurethane and polyvinyl chloride materials, which were added to the base refuse in the test work, was evolved as hydrogen chloride. No free chlorine gas or phosgene was detected.[94]

6.4.1 Vegetation

The effect of hydrogen chloride gas on vegetation has not been studied in any detail. This probably reflects its unimportance as a phytotoxicant. Hydrogen chloride gas is easily scrubbed from flue gases and the major sources are point sources; therefore, it has not been emitted into the atmosphere in large amounts. The incineration of chlorine-containing plastics in large amounts could change this picture unless scrubbers are used.

The effects of hydrogen chloride gas on vegetation were noted in the mid-19th century in the vicinity of alkali plants in Europe and Great Britain.[93] The highest concentration of hydrogen chloride recorded in stack gases was 0.45 mg/m^3 in 1874. No further crop damage due to this gas was reported in Great Britain after the passage of the Alkali Act of 1906. In the United States, damage due to hydrogen chloride gas has been reported by Weiler,[95] Hindawi[96] and Wood.[97] In the USSR, Antipov[98] reported hydrogen chloride gas damage to ornamental plants near a chemical factory that released fumes once or twice a month. Species which were affected included oriental poppy, daisy, belleflower, columbine, bluets, and pylox. Only one study specifically reported the combustion of PVC as the source of the hydrogen chloride gas.[97] Smoke from burning PVC insulation at a wire salvage operation in northern Pennsylvania extensively damaged several northern hardwood species.

Bohne[99] reported hydrogen chloride gas damage to shrubs, trees and flowers near a hospital incinerator.

Not all plants are sensitive to hydrogen chloride gas. Means and Lacasse[100] tested the sensitivity of 12 coniferous and broad-leaf tree species to hydrogen chloride gas. The 4-hour fumigations were conducted under controlled conditions at a temperature of 27°C, relative humidity between 78 and 85 percent, and a light intensity of 1.4×10^4 ergs/cm^2-sec. Under these conditions, the only symptom noted on conifer needles was a tip necrosis on white pine at 8 ppm (20,480 $\mu g/m^3$), on Douglas fir at 12 ppm (30,720 $\mu g/m^3$), and on Norway spruce at 19 ppm (48,640 $\mu g/m^3$). Austrian pine and arborvitae were not injured at concentrations of 18 and 43 ppm (46,080 and 110,080 $\mu g/m^3$), respectively. Symptoms on broadleaf species included marginal and interveinal necrosis and necrotic flecking. Tulip poplar was injured at 3 ppm (7680 $\mu g/m^3$), European black alder and black cherry were injured at 6 ppm (15,360 $\mu g/m^3$), and sugar maple and Norway maple were injured at 7 ppm (17,920 $\mu g/m^3$). Red oak was not injured at concentrations up to 13 ppm (33,280 $\mu g/m^3$).

There are few studies on the effects of vinyl chloride in the environment. In 1962 a study by Heck and Pires[101] found that VC can cause significant injury to plants. Heck and Pires used five different fumigants at three different levels and ranked them in the following order: ethylene > acetylene > propylene > ethylene oxide > vinyl chloride (Table 6.25). The injury symptoms shown for acetylene, propylene, and vinyl chloride were identical to those shown for ethylene. Ethylene is usually considered as a physiologically active gas rather than a toxic gas, such as sulfur dioxide. Ethylene affects a great number of physiological phenomena in plants--such as ripening of fruits, abscission of plant parts, proliferation of tissue, inhibition of growth, and variations in cellular metabolism.[102] Ethylene is a product of plant metabolism, but VC has not been reported from natural sources.

6.4.2 Other Effects

The effects of VC upon microorganisms have not been studied. There has been little work done to determine whether alkynes can be metabolized by microorganisms.[91] Ethylene is adsorbed by soil;[103] VC may be also.

Table 6.25. COMPARISON OF THE TOXICITY LEVELS OF THREE CONCENTRATIONS OF FIVE FUMIGANTS ON SEVERAL PLANT SPECIES[101,a]

Toxicity level	Fumigant	Concentration, ppm
1	Ethylene oxide	1000
2	Ethylene	10, 100, 1000
	Propylene	1000
	Acetylene	1000
3	Acetylene	100
	Vinyl chloride	1000
4	Acetylene	10
5	Propylene	100
	Ethylene oxide	100
	Vinyl chloride	100
6	Propylene	10
7	Ethylene oxide	10
	Vinyl chloride	10

[a] Plants were fumigated for 7 days in each fumigant at each concentration. A qualitative comparison with 1 causing the death of all plants and 7 showing no effect.

A by-product of VC production, EDC tar, has been disposed of by dumping into the North Sea. When EDC tar, a mixture of short-chained aliphatic hydrocarbons, is dumped into the ocean, it gradually sinks. As the tar sinks, the components gradually dissolve in the water. Therefore, relatively little of the tar accumulates in the sediments. It also has a tendency to adhere to a large variety of substances, plankton among them, and form a film or layer around the particles.

Studies by Jernelov et al.[104] indicate that marine animals rapidly accumulate EDC tars from contaminated sea water. An accumulation factor of 2900 was estimated for shrimp *(Leander adspersus)* exposed to 0.01 ppm (25.6 $\mu g/m^3$) EDC tar for 48 hours. Accumulation of low molecular weight compounds of EDC tar is highest from water, whereas the high molecular weight compounds show the greatest accumulation through the food chain. These conclusions are in agreement with the results of studies dealing with chlorinated hydrocarbon (Cl-C) compounds such as DDT in seawater. Dieldrin has also been shown to accumulate rapidly through solution and much less slowly through the food chain.[104] Compared to DDT, PCB, and other Cl-C aromatic substances, the biological half-time is short (1 day to 3 weeks). This suggests that the effects of EDC components might not be as severe as those of DDT, PCB, and other chlorinated hydrocarbons.

Studies made to determine the effects of EDC tars on different stages in the life cycle of the barnacle *Balanus balanoides* L showed that the stage II nauplii were ten times more sensitive than the older stage V and VI larvae.[105] Age, therefore, seems to make the barnacles more resistant to the EDC tars.

In an attempt to determine some physiological aspects of EDC tars at the cellular level, the microorganism *Escherichia coli* was studied.[106] The death of the intact cells was shown to be due to the breakdown of the permeability of the cytoplasmic membrane. The authors suggest that since most known biological membranes are formed according to similar principles, the action of EDC tar on the cell membranes of higher organisms would be similar.

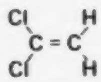
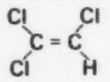
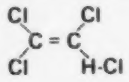
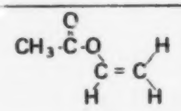
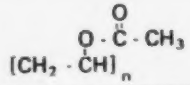
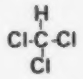
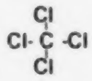
6.5 VINYL CHLORIDE-RELATED COMPOUNDS AND OTHER CHEMICAL CARCINOGENS

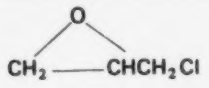
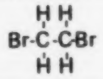
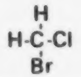
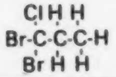
6.5.1 Related Compounds

The compelling evidence of the carcinogenicity of VC from both an epidemological and toxicological standpoint raises the question of the possible carcinogenicity of other related chemicals in the ambient air. Production figures and major uses for chemicals of industrial importance with structure similar to vinyl chloride are summarized in Table 6.26.[107-109] Compounds similar in structure and metabolism to vinyl chloride have not been adequately studied for possible carcinogenicity. The following are examples of such compounds:

- 1,1 dichloroethylene (vinylidine chloride)–This is a known potent hepatotoxin, which acts quite rapidly. Workers at the B. F. Goodrich plant in Louisville who developed angiosarcoma of the liver were exposed to 1,1-DCE as well as to vinyl chloride. No information is available at present on workers exposed only to 1,1-DCE for their working lifetimes. When fasted rats were exposed to 0.02 percent 1,1-DCE, serum alanine-ketogluterate transaminase (AKT) activity was elevated about 50 fold at 2 hours after the end of a 4-hour inhalation exposure. Exposure of fasted rats to 0.1 percent VC was without effect on serum AKT.[110] There is some preliminary evidence of carcinogenicity in animals but this has not yet been reported in the literature.
- 1,2 dichloroethylene–No data available.
- Trichloroethylene–Preliminary evaluation of a recent study in mice has shown cancer of the liver and other organs.[111]

Table 6.26. PRODUCTION AND USE IN THE UNITED STATES OF CHEMICALS RELATED TO VINYL CHLORIDE AND POLYVINYL CHLORIDE

Chemical	Structure	Production (year), million kilograms	Major uses
1, 1-dichloroethylene (vinylidine chloride)			Monomer for vinyl chloride copolymer and polyvinylidine chloride
Trichloroethylene		197 (1972)[107]	Metal degreasing, manufacturing solvent
Tetrachloroethylene (perchloroethylene)		335 (1972)[107]	Dry cleaning, metal, degreasing, chemical intermediate
Vinyl acetate		328 (1969)[108]	Polymer production
Polyvinyl acetate		189 (1970)[107]	Textile sizing, adhesives, paper coating, polymerization aid
Chloroform	 $\overset{H}{\underset{Cl}{Cl\text{-}C\text{-}Cl}}$	108 (1970)[107]	Mainly as a refrigerant and aerosol propellant, pharmaceuticals and toiletries
Carbontetrachloride	 $\overset{Cl}{\underset{Cl}{Cl\text{-}C\text{-}Cl}}$	455 (1970)[107]	Manufacture of dichlorodifluoromethane (320 million kg) and trichlorofluoromethane (120 million kg)

Epichlorohydrin		Not available	Solvent for natural and synthetic resin linking agent in the crease proofing of textiles, paper processing, water proofing of materials.
Dibromoethane	 $\mathrm{Br{-}\overset{H}{\underset{H}{C}}{-}\overset{H}{\underset{H}{C}}{-}Br}$	140,000 (1969)[109]	Used extensively in antiknock gasoline. Also used as pesticide
Chlorobromomethane	 $\mathrm{H{-}\overset{H}{\underset{Br}{C}}{-}Cl}$	Not available	Fire extinguishing agent and chemical intermediate
Chlorodibromopropane	 $\mathrm{Br{-}\overset{Cl}{\underset{Br}{C}}{-}\overset{H}{\underset{H}{C}}{-}\overset{H}{\underset{H}{C}}{-}H}$	Not available	

- Tetrachloroethylene (perchloroethylene)–Various animal species were exposed for 7 hours a day to 100 to 2500 ppm (256 to 6400 mg/m^3) for up to 250 days. No tumors were discovered.[112] No long-term followup studies of exposure in man have been conducted.

- Epichlorohydrin–Considered to have carcinogenic potential. Mutagenicity has been demonstrated in drosophila neurospora, E. coli, and barley.[113-121]

- Carbon tetrachloride–Has produced liver tumors in the mouse, hamster, and rat following several routes of administration including inhalation and oral ingestion. Cases of hepatomas have appeared in man in several years after carbon tetrachloride poisoning was reported.[122]

- Chloroform–The carcinogenicity of chloroform has been investigated only in mice in experiments involving a small number of animals at risk, but among these the frequency of liver tumors was high. No long-term followup studies in men exposed to chloroform have been reported.[122]

- 1,2 dibromoethane–A severe irritant. Necrosis of liver and kidney is not conspicuous, although fatal liver damage has been reported.[123] Exposure of bacteria to levels of DBE exceeding 0.04 *M* resulted in cellular death accompanied by cell lyses. A DBE concentration of 0.015 *M* was bacteriostatic for the first hour and bactericidal for the next 4 hours. Of the metabolism processes tested, RNA synthesis was the most susceptible to inhibition by DBE. The authors hypothesize that 1,2-DBE possesses a neurotropic carcinogenic potential.[124]

- Chlorobromomethane–Has proved to be more toxic than carbon tetrachloride in acute exposures and less toxic in chronic ones. Both liver and renal injuries have been noted.[124]

- Chlorodibromopropane–No data available.

- Polyvinyl chloride–Film was implanted in various locations in rats for up to 18 months. Several tumors were observed, all in the area of the implant.[125]

- 1,1,2 trichloropropene–Rabbits were dosed orally with compound in oil at 0.1 LD_{50} for 6 months. There was evidence of changes in lymph nodes after 18 months.[125]

- Vinyl alcohol polymer–Implants of polymer sponges at various locations in rats for the life span gave many sarcomas at the site of implantation and a few tumors at other locations.

- Vinyl chloride acetate copolymer–Implants in rats gave formation of tumors only at the site of implantation.[125]

For the most part, toxicological studies of chemicals related to VC have been limited to acute studies, with only minor emphasis on long-term or carcinogenic effects. When carcinogenic studies were undertaken, they involved, in general, exposures that were too short or included too limited a number of animals to provide conclusive negative results.

6.5.2 Other Carcinogens in Polluted Community Air

The array of contaminants identified in polluted community air includes other chemical and physical agents–such as polycyclic aromatic hydrocarbons, azaheterocyclic hydrocarbons, certain metal compounds, asbestos, and certain radionuclides–that are either proven or highly suspect carcinogenic hazards.[126,127] However, very few definitive studies have been conducted to determine epidemiologically the contribution of these ambient pollutants to human carcinogenesis. One of the observed epidemiologic characteristics of the world-wide increase in lung cancer is the higher incidence in urban residents. Although other factors–such as population density and occupational differences–may contribute to urban and rural differences, an urban-rural difference in lung cancer rates persists even after correction for these factors.

Additional support for a probable etiological role for ambient chemical carcinogens in lung cancer can be gained from several studies undertaken to measure the effects of population migration on lung cancer risk.[128,129] These studies in migrants have shown that either increases or decreases in lung cancer are compatible with changes in environment. The changes in rates parallel the general population concentrations in the areas under study and persist after correction for cigarette smoking, although at a reduced level. Moves from high pollution to low pollution regions reduced lung cancer death rates and vice versa (Table 6.27). Within the United States and Great Britain, studies show a gradient of risk to lung cancer from low in rural to high in urban areas. Migrants from rural to urban areas in the United States appear to increase their lung cancer rates.

In a recent article, Kotin[126,127] draws attention to certain observations on the nature of carcinogens which should be considered when initiating studies of carcinogenesis associated with air pollutants:

- Cancer induction most frequently requires prolonged periods of exposure to carcinogenic agents.
- Cancer can be caused by several carcinogenic agents acting in combination either in an additive, synergistic, or inhibitory relation to one another. This is particularly relevant to lung cancer where a variety of ubiquitous environmental exposures to carcinogenic agents exist.
- The action of a carcinogenic agent in lung cancer induction may be determined by the competency of the host's defenses at the anatomic, physiological, and biochemical levels. Polluted community air contains a large variety of chemical and physical irritants, which though unable to cause cancer, facilitate the action of carcinogenic agents by attenuating or destroying the effectiveness of the mucociliary apparatus of the lining of the lung. This facilitates deposition and retention of particles carrying carcniogenic agents. In addition, these irritants can induce changes in the epithelium (metaplasia) which may enhance the progression of changes to cancer. These irritants may alter the metabolic handling of carcinogenic agents and thereby enhance their cancer-inducing potency.
- There is evidence that, at the cellular level, environmental chemical cofactors of a highly nonspecific nature may work together with chemical carginogens to increase their effectiveness.

Vinyl chloride may be viewed as an excellent example of a chemical carcinogen in air. It may be just one of many such compounds, although the potential carcinogenicity of the others has not yet been identified.

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Table 6.27. AGE ADJUSTED DEATH RATES FROM LUNG CANCER IN GREAT BRITAIN, NORWAY, AND THE UNITED STATES[129-131]

Population group	Lung cancer death rate (per 100,000 persons)	
	Males	Females
Great Britain residents	151.2	19.3
Great Britain-born U.S. residents	93.7	11.5
Norway residents	30.5	5.6
Norway-born U.S. residents	47.5	10.7
Native U.S. residents	72.2	9.8

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7. CONTROL TECHNOLOGY AND REMEDIAL ACTIONS

7.1 INTRODUCTION

Most of the presently used or available technologies for controlling VC emissions are a basic part of the processing system and serve to recover reactant or product. These controls are appraised herein either by using performance data from selected VC and PVC manufacturing plants, or by comparing emission levels for plants with and without controls. The controls so appraised for VC production include: recycling of vent streams, condensation with refrigeration, adsorption to carbon, incineration, absorption (scrubbing), and venting to flares. Monomer loading and unloading involves special additional controls: vapor collection adapters with recycling, thermal level detectors with recycling, and magnetic gauges. Polymer production can possibly benefit from application of controls indicated for the monomer production in addition to vacuum stripping, steam stripping, and the recovery of the stripped monomer.

A qualitative assessment of the potential applications of selected controls has been made based upon information presented by a few U.S. industrial firms.[1] The results of this assessment are summarized for each process in the following paragraphs. All percent reductions of emissions are estimates.

7.2 MONOMER PRODUCTION

The available data on emissions from monomer production seem to point to a present total emission of about 0.45 kg per 100 kg of VC produced. To this amount should be added a smaller, intermittent loss of VC in the loading area.

A reduction in emissions can be obtained by refrigeration and/or absorption of vinyl chloride in the vents by appropriate solvents (ethylene dichloride, EDC, for instance), or by combustion of the organics in vent streams, followed by removal of the HC1 produced. Ninety-nine percent control represents the approximate maximum reduction available for industrial point sources with present-day (1975) technology. To ensure such a reduction, vent losses in the loading area must be controlled.

7.2.1 VC from Acetylene and Hydrogen Chloride (HCl)

This route for producing VC is based on acetylene. A second route based on ethylene will be discussed later. Vinyl chloride from acetylene is the older technology and suffers an economic penalty. As of the summer of 1975, no producers were known to be operating an acetylene-based plant.

The reactor vent is the main emissions source for the acetylene and HCl process, accounting for 60 percent of total emissions. Condensation at 4.4°C (40°F) and 0.24×10^6 N/m^2 (35 psig) is now used. Addition of refrigeration would decrease emissions by about 50 percent. If an HCl scrubber were also used, the combined controls should achieve 85 percent reduction. With carbon adsorption, emissions might be reduced by 99 percent. Recycling does not appear to be applicable.

Fugitive emissions and tank car loading, unloading, and accidents account for about 25 percent of total emissions from this process. Use of diaphragm valves, replacement of packed pump seals with pressurized mechanical seals, use of vapor collectors on samplers, and preventive maintenance can be expected to reduce these emissions by 50 to 95 percent.

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Incineration, with HCl recovery, should reduce condenser vent losses 99 percent. Thermal-level detectors combined with vent gas refrigeration and/or recycling would reduce slip gauge emissions by 95 percent. Replacing the slip gauge with a magnetic gauge could reduce the emissions by nearly 100 percent. Vapor-collector adapters with recycling would reduce purge losses 50 to 90 percent. Incineration should reduce loading air emissions about 90 percent.

7.2.2 VC by Ethylene-based Technology

Ethylene-based technology consists of basically two processes which combine to produce VC from chlorine, ethylene, and air (oxygen). In the direct process, the EDC is made from ethylene and chlorine; in the second process, oxychlorination is used for making EDC from C_2^{2-}, HCl, and oxygen. The EDC intermediate product is cracked to VC during dehydrochlorination, and the by-product HCl stream is recycled to the oxychlorination reactor. The combination of processes is commonly referred to as the balanced process.

Major emission sources of VC in this process are from the EDC light-ends column vent (9 to 20 percent), the EDC heavy-ends tar removal column vent (18 percent), the VCM light-ends column vent (10 to 13 percent), tank car loading (10 to 20 percent), and oxychlorination reactor vent (6 to 10 percent). The distillation vents could be controlled by incineration or condensation with recycle.

EDC light-ends column emissions could be reduced about 50 percent by using refrigerated condensers and nearly 100 percent with carbon adsorption. The adsorbed organics would then have to be disposed of; incineration is one means of disposal. Recycling to a post chlorination unit would be almost 100 percent effective.

Heavy-ends column emissions are believed to be controllable by incineration (90 percent reduction), and by adsorption (close to 100 percent reduction); again, the adsorbed organics would have to be disposed of.

VC light-ends column vent emissions would require adsorption or incinceration, either of which is capable of nearly 100 percent reduction.

The tank car loading controls given in Section 7.2.1 would apply here also.

The oxychlorination reactor vent emissions on some processes could be reduced by using additional chlorination. If oxygen is fed instead of air, the fluidized bed systems will produce a vent stream that is combustible without supplemental fuel. Several experimental processes are in development stages using vent gas recycle with oxygen feed and catalytic incineration.

7.3 POLYMER PRODUCTION

In the production of polyvinyl chloride, present monomer losses in kilograms per kilogram of product are at least an order of magnitude higher than in the production of VC. Most producers report about a 3 to 4 percent lower PVC production than monomer intake. From some data submitted by manufacturers, 0.01 to 0.3 percent of PVC made is lost. A portion of this is emitted as fine particulate to the atmosphere. The actual monomer emission is therefore in the order of 3 to 3.7 percent. These losses result from the batch nature of the polymerization operation and from the drying of the polymer, if practiced. Reduction of these losses poses a more difficult problem than those encountered in VC plants. A reduction to 80 percent of the present level of losses seems possible, but a 95 percent reduction of the total emissions in some of the existing polymer plants without process changes might be beyond present techniques at acceptable costs. However, if intensive stripping of the suspension at the end of the reaction is allowable, the 95 percent reduction might be feasible.

The move to progressively bigger reaction vessels should be noted. One company has studied this development and is proposing the use of a 454 m^3 (120,000 gal) polymerization reactor as compared to the present typical size reactor of 19 to 38 m^3 (5000 to 10,000 gal). A possible emergency blowing of such a reactor might, however, lead to very high peak values of vinyl chloride emissions.

This report has not considered the influence of VC remaining in the polymer. Polymer is now being offered for sale with VC residual content of less than 10 ppm (10 mg/kg). The residual monomer is mostly released during further processing and might thus create emission problems during fabrication processes, particularly those involving heat. EPA is now sponsoring a study to determine the emissions from fabrication processes.

7.3.1 Suspension Polymerization

Fugitive emissions throughout the suspension polymerization process account for an estimated 45 percent of VC emissions. However, a good maintenance program and minor equipment modifications should reduce fugitive emissions by about 50 percent.

Vacuum stripping of the crude product would be 95 percent efficient for reducing emissions from sources downstream of the stripper. Carbon adsorption, incineration, or absorption could reduce emissions by the same amount; condensation with refrigeration, 50 to 70 percent.

Collectively, vents from the dryer, the air conveyor, the storage site, and wash water provide 35 percent of the total emissions. Vacuum stripping and absorption are expected to give 95 percent reduction; and recycles to compressors, 40 to 60 percent reduction in emissions from these sources.

7.3.2 Emulsion Polymerization

The dryer vent, air conveyor vent, site storage vent, and waste-water vent appear to account collectively for about 85 percent of total emissions from emulsion polymerization. Carbon adsorption and steam stripping could reduce these emissions by 50 to 95 percent. Fugitive losses contribute 17 percent of the emissions; blend surge tank vents contribute another 6 percent. Vacuum stripping, if practiced, would effect 90 to 95 percent reduction; carbon adsorption, 50 to 95 percent. Condensation with refrigeration would reduce either source about 40 to 60 percent. Absorption is expected to reduce both losses 50 to 80 percent. Preventive maintenance would reduce fugitive losses 25 to 50 percent.

7.3.3 Bulk Polymerization

During bulk polymerization, the VC reactor vents (25 percent), fugitive emissions (35 percent), and the combined resin receiver, collector, and storage (20 percent) are the major emission sources. For the reactor vent, adsorption (50 to 90 percent reduction) and incineration (50 to 90 percent reduction) are indicated for control purposes. Intensive maintenance is believed to be capable of giving 50 to 75 percent reduction of the diverse and ill-defined fugitive emissions. The product-collection systems vents could be water-washed, then adsorbed (50 to 90 percent reduction) or incinerated (50 to 90 percent reduction).

7.3.4 Solution Polymerization

While limited data are at present available for this process, it is expected to have the emission characteristics of the suspension process (Section 7.3.1) and to respond roughly to the same controls.

7.4 REFERENCE FOR SECTION 7

1. Vinyl Chloride—Assessment of Emission Control Techniques and Costs. U.S. Environmental Protection Agency, Washington, D.C. Publication No. EPA-650/2-74-097. September 1974. 84 p.